



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : C07C 237/04, A61K 31/16, 31/40, 31/415, C07C 237/22, 323/60, 317/48, C07D 207/40, 207/26, 233/88, 233/86, C07C 235/22, 335/16, 335/08, 255/56, 255/60, 275/30, C07D 207/36, C07M 5/00, A61P 5/00</p>	A2	<p>(11) International Publication Number: WO 00/37430</p> <p>(43) International Publication Date: 29 June 2000 (29.06.00)</p>
<p>(21) International Application Number: PCT/US99/26862</p> <p>(22) International Filing Date: 12 November 1999 (12.11.99)</p> <p>(30) Priority Data: 09/215,351 18 December 1998 (18.12.98) US</p> <p>(71) Applicant: BIOPHYSICA, INC. [US/US]; 3333 North Torrey Pines Court #100, La Jolla, CA 92037 (US).</p> <p>(72) Inventors: SOVAK, Milos; 3333 North Torrey Pines Court #100, La Jolla, CA 92037 (US). SELIGSON, Allen, L.; 1770 Deavers Drive, San Marcos, CA 92061 (US). DOUGLAS, James, Gordon, III; 4066 Moratalla Terrace, San Diego, CA 92103 (US). CAMPION, Brian; 959 North Vulcan Avenue, Leucadia, CA 92024 (US). BROWN, Jason, W.; 4950 Santa Cruz Avenue, San Diego, CA 92067 (US).</p> <p>(74) Agent: RAE-VENTER, Barbara; Rae-Venter Law Group, P.C., P.O. Box 60039, Palo Alto, CA 94306-0039 (US).</p>	<p>(81) Designated States: AU, CZ, HU, IL, JP, NO, PL, SK, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: USE OF ANDROGEN RECEPTOR SUPPRESSORS</p> <p>(57) Abstract</p> <p>Substituted phenylalanines are provided comprising an hydantoin, urea or 2-hydroxyl, 2-methylpropionyl group, dimers thereof and alkyl, polyfluoroamido and haloaryl amino derivatives thereof, as well as radiolabeled derivatives thereof. The compounds bind specifically to the androgen receptor and find use in indication associated with the androgen receptor, such as cell hyperplasia dependent on androgens, hirsutism, acne and androgenetic alopecia.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

USE OF ANDROGEN RECEPTOR SUPPRESSORS

Technical field

10 The field of this invention is compounds and their use in the treatment of prostate cancer and hyper-androgenic syndromes including alopecia, hirsutism and acne vulgaris.

Background

15 The existence of a number of pathologic syndromes depends on androgen hormones. Thus, growth of prostate cancer in early stages is androgen driven and can, at least temporarily, be stopped by androgen deprivation. Androgenic alopecia is caused by an unexplained switch from the growth promoting effect of androgens on the hair follicles to hair loss. In skin androgen mediated disorders, such as alopecia, acne vulgaris, and hirsutism, excess of the cutaneous androgens were shown to be the major nosological factor.

20 The androgenic hormones can act only via an androgenic receptor (AR), which is a transcription factor, a protein which interacts with a specific region of DNA. Thus, the mode of action of testosterone and its much more potent analog, 5-alpha dihydrotestosterone (DHT) depends upon binding to the AR. Only then can transcription by RNA polymerase II take place.

25 In the treatment of androgenic alopecia, various antiandrogens originally developed for the treatment of prostate cancer were claimed for systemic use, but side effects of chronic therapy with these systemically absorbable substances were of concern. In cutaneous afflictions anti-androgenic compositions have been tried, but with limited success, possibly because all non-steroidal compounds are resorbed by the skin and elicit systemic effects, which prevents their use in males. In the scalp, the precursors to androgens are normally converted into potent androgens, which bind
30 to the AR in the hair follicles and promote hair growth. In genetically pre-disposed subjects however androgens at certain age cause hair loss. Clearly, a topically active composition capable of cutaneous, but not systemic resorption, and of suppressing or eliminating the AR locally, would be useful in preventing or reversing the incipient androgenic alopecia.

35 The current state of prostate cancer therapy (CaP), the second most prevalent malignancy in males, is unsatisfactory. When detected early, with the tumor strictly confined to the prostate gland, CaP can be often controlled by implantation of radioactive seeds, or by prostatectomy, which often

results in incontinence and impotence. Locally advanced prostate cancer can often be reasonably controlled when in the pelvis and is encompassed into a single port of an external radiation beam.

For advanced CaP, the standard treatment is androgen receptor- blockade. usually in combination with LHRH superagonists, which suppresses both adrenal and testicular testosterone.

5 The rationale of this approach is that early prostate cancer invariably depends on androgens for growth. The activity mechanism of clinically utilized antiandrogens is thought to involve blockade of the AR by binding to it and/or by interference with binding of the AR to the DNA; some agonistic compounds can even promote DNA binding but they do modify the binding domain. Thus, cyproterone acetate was found to block about 50% of AR binding to the DNA, while flutamide, bicalutamide or nilutamide, were found to completely block such binding. All of these state of the
10 art compositions have nevertheless only limited applicability, as the primary tumor and its metastases eventually become hormonally refractory and resistant to further anti-androgenic therapy.

The reason is invariably AR mutation, which can be occasionally found as a genetic deviation. but is usually a result of the AR blockade. Even when both suprarenal and testicular androgens are
15 eliminated by chemical castration, using LHRH super agonist and/or by surgical castration, the mutated receptor retains the capability to be activated by various steroidal metabolites and even progestins and estrogens. A variety of other factors can activate the androgen receptor gene via AR activation, such as insulin-like growth factor, epidermal growth factor, and keratinocyte growth factor and neuroendocrine transmitters, such as serotonin. Therefore, blocking the AR is not an ideal
20 treatment and a new approach is needed. It has also been shown that as a result of the AR blockade, the AR gene is amplified with the resulting overproduction of the AR. In 6 to 24 months the AR mutates and the tumor and metastases became hormone refractory and continue to grow.

The common denominator of resistance to current anti-androgens is a modification of the AR. Even after a relapse following androgen blockade therapy, experiments indicate the AR is still
25 present and plays a major role in the propagation of CaP cells.

In selecting therapeutic options, a correct therapeutic decision can only be made if the extent of the disease is known. When CaP is confined strictly to the gland, surgery and/or local or external radiation can be curative. However, in the case of extracapsular disease, prostatectomy or radiation are not only useless, but noxious, since a high rate of serious side effects, such as impotence, incontinence and chronic inflammation of the adjacent tissues accompanies these interventions.
30 Members of the current diagnostic armamentarium comprise digital rectal palpation, serum prostate

specific antigen determination and ultrasound, magnetic resonance or x-ray imaging. These techniques cannot reliably detect CaP spread into the soft tissues. Thus, metastases to the lymph nodes cannot be reliably detected with these methods resulting in clinical understaging of 40 to 60% of the instances.

5 The prior art of diagnostic localizing agents for CaP teaches specific radioactively labeled antibodies, but widespread use is limited by the complexity of the procedure. 5 α -dihydrotestosterone labeled with ^{18}F has been used for PET scanning, a generally inaccessible imaging modality.

There are, therefore, substantial deficiencies in both therapeutic and diagnostic approaches
10 to the treatment of CaP. It is therefore of interest to find compounds which not only block the AR, but also diminish the number of ARs which are available. In addition, another desirable characteristic for topical purposes would be compounds which have low or no systemic resorption. Also, the compounds should degrade or be metabolized into components of low or no toxicity and have little or no anti-androgenic activity. In addition, radioisotope labeled compounds specific for
15 neoplastic prostate cells would be of great help. These compounds would allow the physician to visualize the pathomorphology of CaP accurately, so that unnecessary and costly surgery and/or radiation is avoided in patients where CaP has progressed beyond the reach of curative surgery or the scope of a single radiation port. Other appropriate therapies, such as androgen ablation and/or unspecific chemotherapy, can then be instituted.

20 Relevant Literature

U.S. Patent No. 5,656,651 and WO97/00071, and references cited therein, describe anti-androgenic directed compositions based on phenyldimethylhydantoins, where the phenyl group is substituted with a trifluoromethyl group and either a cyano or nitro group. See also, Battmann et al.,
25 J. Steroid Biochem. Molec. Biol. 64:103-111 (1998); Cousty-Berlin, ibid 51:47-55 (1994); and Battmann et al., ibid 48:55-60 (1994), for a description of analogous compounds and their activity. For other compounds having the substituted phenyl moiety, see U.S. Patent nos. 4,636,505 and 4,880,839, and EP 0 100 172. For discussions about the activities of antiandrogens, see Kuil and Brinkmann, Eur. Urol. 29:78-82 (1996); Kondo et al., Prostate 29:146-152 (1996), and Simard, et al.,
30 Urology 49:580-589 (1997). For discussions about alopecia and its relationship with androgens, see Kaufman, Dermatologic Clinics 14:697-711 (1996); Toney et al., J. Steroid Biochem. Molec.

Biol. 60:131-136 (1997); Brouwer et al., J. of Dermatology 137:699-702 (1997); and Shapiro and Price Dermatologic Clinics 16:341-356 (1998).

SUMMARY OF THE INVENTION

5 Compositions and their method of use are provided, where the compositions are substituted-phenyl-2-methyl,2-(hydroxy or methyl)-3-heteroatom substituted-propionamide derivatives, having heterolinked perfluoroacyl or haloaryl substituents or being bis-derivatives, where the substituent group may be linked to the heteroatom directly or by a linking group. The compounds are active anti-androgenic compounds and find use in the treatment of neoplasms and alopecia dependent on
10 androgen hormones. In addition, the compounds may be radioisotope labeled for use in therapy and diagnosis.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

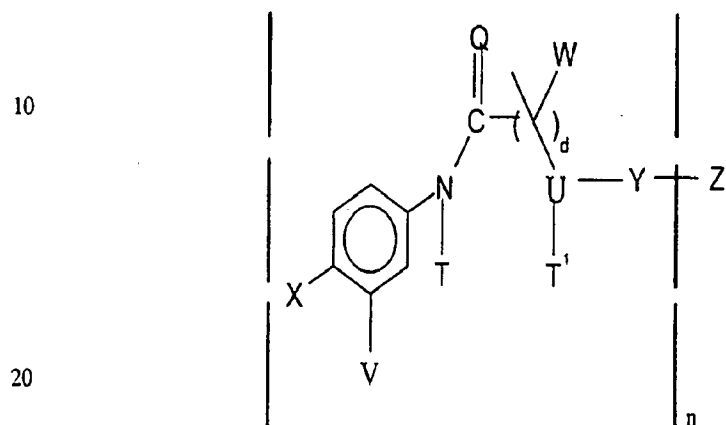
Compositions are provided which are characterized by having an aniline group which has
15 at least one substituent at the para position, desirably a second substituent at the meta position, and to which the aniline nitrogen is bonded a 2-methyl,2-(hydroxy or methyl)-3-heteroatom substituted-propionyl or N-substituted carbamoyl, particularly thiocarbamoyl. The heteroatom (including the nitrogen of the carbamoyl group) is linked through a bond or linking group to a perfluoroacyl, haloaryl, or alkyl substituent or to a divalent linking group to form a bis-compound. The compounds
20 have individual or collective characteristics associated with cellular toxicity, diminution of androgen receptors on the surface of cells and low systemic resorption when administered topically. In addition, the compounds may be radioisotope labeled, to be used in diagnosis and therapy.

The monomeric compounds will generally be of from at least 12 carbon atoms, usually at least 14 carbon atoms, more usually of at least 16 carbon atoms and not more than about 36 carbon
25 atoms, usually not more than about 28 carbon atoms, while the bis-compounds will usually be at least 20 carbon atoms, usually at least 22 carbon atoms and not more than about 40 carbon atoms. usually not more than about 36 carbon atoms.

The two position of the propionamide has two methyl groups or one methyl and one hydroxy group. The perfluoroacyl group will be linked to the 3-heteropropionamide through the heteroatom
30 by a bond or a linking group of from 1 to 10, usually 2 to 8 carbon atoms and from 0 to 6, usually

0 to 4, more usually 0 to 2 heteroatoms in the chain of the linking group. The linking group may be aliphatic, alicyclic, heterocyclic or aromatic, usually aliphatic, more usually saturated aliphatic.

For the most part, the compounds of this invention will have the following formula:



wherein:

25 Q is chalcogen (oxygen or sulfur);

X is nitro (NO₂), cyano (CN), or halogen, particularly of from atomic no. 9 to 35, particularly 9 to 17 (fluorine and chlorine);

V is CF₃, halogen, particularly of from atomic no. 9 to 35, particularly 9 to 17 (fluorine and chlorine) or H; usually CF₃;

30 T is hydrogen or is taken together with T¹ to form a C=Z bridge, where Z is chalcogen of atomic number 8 to 16 (oxygen {carbonyl} or sulfur {thiocarbonyl}), particularly sulfur;

W is OH when T is H and methyl when T and T¹ are C=Z;

U is N when T and T¹ are taken together to form a C=Z bridge or when d is 0, and is otherwise taken together with T¹ to form a bond or NH, S or O, particularly NH and S;

35 n is 1 or 2 and d is 0 or 1;

when d is 0, T and T¹ are hydrogen;

when d is 1, then:

when n is 1 or when d is 0, Y is a bond or linking group of from 1 to 10, frequently 0 to 8 carbon atoms, usually 2 to 8, more usually 2 to 6 carbon atoms and from 0 to 6, usually 0 to 4 heteroatoms, with from 0 to 4 heteroatoms in the chain, where the heteroatoms are N, O, S, and the

40

heteroatoms are present as amino (includes amido), oxy and oxo- and non-oxo-carbonyl, and thio and thiono- and non-thiono-carbonyl, where the linking group may be aliphatic, alicyclic, heterocyclic or aromatic, usually aliphatic, usually saturated; and

Z, when not taken together with Y, is an alicyclic group of from 1 to 10, usually 1 to 6, more usually 1 to 5 carbon atoms, saturated or unsaturated, e.g. double or triple bond, polyfluoroacylamido group of from 2 to 10, frequently of 2 to 8, usually 2 to 6, more usually 3 to 5 carbon atoms and having at least 2 fluoro groups and a total of $2m-1$ fluoro groups, usually having at least $2m-2$ fluoro groups, wherein m is the number of carbon atoms, or substituted arylamino of from 6 to 12, more usually 6 to 10 carbon atoms, particularly anilino, and halogen of atomic number from 9 to 80, particularly F, Cl, Br and I, more particularly Br and I (atomic no. 35 to 80), particularly para substituted;

when n is 2, Y and Z are taken together to form a bond or a linking group of a total of from 1 to 10, usually 1 to 8 atoms, having 0 to 10, usually 0 to 8 carbon atoms, more usually 2 to 6 carbon atoms and from 0 to 6, usually 0 to 4 heteroatoms, with from 0 to 4, usually 0 to 2, heteroatoms in the chain, where the heteroatoms are N, O, S, there being at least one carbon atom or heteroatom in the linking group, and the heteroatoms are present as amino (includes amido), oxy and oxo- and non-oxo-carbonyl, and thio and thiono- and non-thiono-carbonyl, where the linking group when other than 1 heteroatom may be aliphatic, alicyclic, heterocyclic or aromatic, usually aliphatic, usually saturated; and

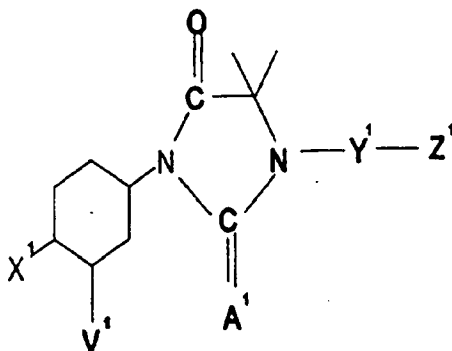
the phenyl group, Y and/ or Z may be substituted with convenient radiolabel, particularly Z, where the label may be radioactive iodine, chelated technetium, or other suitable emitter.

When Y is a bond, U will also usually be a bond, so as to join the nitrogen of the polyfluoroacylamido or anilino group to the propionyl carbon atom.

For radiolabeling, Z may have different convenient functionalities depending on the nature of the radiolabel. For example, with radioactive iodine, one may use an acetylenic group for addition a hydride, e.g. a tin hydride, followed by substitution of the tin group with iodine. Where the radiolabel is chelated, the chelating group may be attached to Z by any convenient functionality, such as an amide group, ester, ether, thioether, amino, etc. Chelating compounds include combinations of imidazoles, thiolacetic acids, cysteine, glycineamides, etc.

The compounds may or may not have one or more stereoisomeric centers. The compounds may be used as racemic mixtures or be resolved in their enantiomers and used as enantiomers.

When the compounds have the hydantoin ring, they will usually come within the following formula:



wherein:

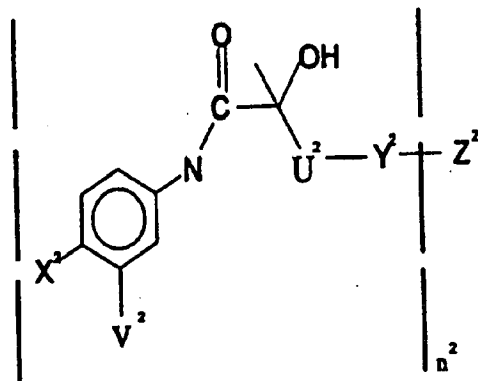
X^1 , V^1 , and Y^1 come within the definitions of X , V and Y , respectively;

Y^1 is usually alkylene of from 2 to 10, usually 2 to 8, more usually 2 to 6, carbon atoms;

A^1 is chalcogen (oxygen or sulfur), particularly sulfur; and

Z^1 is a polyfluoroacylamido of from 2 to 10, usually 2 to 6, more usually 3 to 5 carbon atoms and having at least 2 fluoro groups and not more than $2m-1$ fluoro groups, usually having at least $2m-2$ fluoro groups, wherein m is the number of carbon atoms, or substituted arylamino of from 6 to 12, more usually 6 to 10 carbon atoms, particularly anilino, and halogen of atomic number from 9 to 80, particularly F, Cl, Br and I, more particularly Br and I (atomic no. 35 to 80) preferably para-substituted

Those compounds which have an 2-hydroxy, 2-methylpropionyl group as a moiety will for the most part have the following formula:



wherein:

X^2 , V^2 and n^2 come within the definitions of X , V and n , respectively;

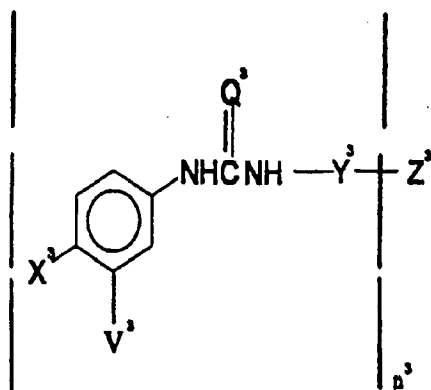
U^2 is a bond or heteroatom, particularly nitrogen and chalcogen (O and S);

when n^2 is 1;

Y^2 is an alkylene group of from 1 to 10, usually 1 to 6 carbon atoms, more usually 2 to 6 carbon atoms and 0 to 4 heteroatoms, which heteroatoms are N and chalcogen and include the functional groups carbonyl, thiocarbonyl, oxy, thio, and amino; and

Z^2 is a polyfluoroacylamido of from 2 to 10, usually 2 to 6, more usually 2 to 4 carbon atoms and having at least 2 fluoro groups and not more than $2m-1$ fluoro groups, usually having at least $2m-2$ fluoro groups, or substituted arylamino of from 6 to 12, more usually 6 to 10 carbon atoms, particularly phenyl, and halogen of atomic number from 9 to 80, particularly F, Cl, Br and I, more particularly Br and I, preferably para substituted.

The compounds which have the carbamoyl group, will for the most part have the following formula:



wherein:

X^3 and V^3 come within the definitions of X^1 and V^1 ;

Q^3 is chalcogen, particularly sulfur;

Y^3 is a bond or alkylene group of from 1 to 6, usually 1 to 3 carbon atoms;

Z^3 is alkyl of from 1 to 6 carbon atoms, a polyfluoroacylamido of from 2 to 10, usually 2 to 6, more usually 2 to 4 carbon atoms and having at least 2 fluoro groups and not more than $2m-1$ fluoro groups, usually having at least $2m-2$ fluoro groups, or substituted arylamino of from 6 to 12,

more usually 6 to 10 carbon atoms, particularly phenyl, and halogen of atomic number from 9 to 80, particularly F, Cl, Br and I, more particularly Br and I, preferably para substituted.

The subject compounds can be prepared in accordance with conventional ways, varying the particular procedure based on the particular side groups. The preparation of hydantoins conveniently involves the use of an isocyanate and a substituted α -aminoacetonitrile. By appropriate choice of the isocyanate and the α -aminoacetonitrile, one may arrive at the final product in a single step. Alternatively, one may employ various protective groups, which may be subsequently removed or provide for substituents which become involved in the formation of the hydantoin or may provide for sites for further derivatization. Various procedures are described in EPO Publication nos. 0 494 819 and 0 580 459. The urea compounds may be prepared using an isocyanate (including thioisocyanate) and an amino compound. A significant number of examples are provided for the hydantoins and the propionyl moiety compounds in the experimental section of this application.

The subject compounds can be used as antiandrogens, substituting for known antiandrogens in the treatment of proliferative diseases, hirsutism, acne and androgenetic alopecia. The subject compounds display one or more of the following properties: specific binding and high affinity to the androgen receptor; destroying or suppressing the presence of the androgen receptor in a concentration dependent fashion; low or no systemic resorption when applied topically; and limited stability, degrading into components of low toxicity and no androgenic activity. The subject compounds may be used individually or in combination and with other antiandrogens or other treatments, such as flutamide, bicalutamide and nilutamide, irradiation, heat, or the like, as may be conventionally employed and as may be moderated for use in conjunction with the subject compounds. The treatments may be performed concurrently, consecutively or in accordance with a predetermined regimen to minimize the likelihood of neoplastic cell refractoriness.

The subject compounds are found to have high cytostatic and cytotoxic activity, inhibiting cell growth and viability of cells having an androgen receptor. They also have substantially greater effect against neoplastic cells, as compared to normal cells.

Therapeutic compositions can be formulated in accordance with conventional ways and the indication to be treated. The composition may be formulated for oral or parenteral, e.g. intravascular, subcutaneous, intratumoral, intraperitoneally, etc., administration, as a pill, powder, capsule, aqueous or oily solution or dispersion, or the like. Conventional carriers include saline, phosphate buffered saline, water, vegetable oils, ethanol, isopropanol, etc. Excipients, buffers,

stabilizers, flavorings or the like may be employed. The concentration may be from about 0.1 to 10 weight % and at a dosage in the range of about 0.1mg to about 5g, usually not more than about 2g/dose. One or more doses may be given daily.

The subject compounds may be used in conjunction with conventional therapeutic agents for a specified treatment, being used in combination with anti-neoplastic agents, agents for the treatment of alopecia, etc. Of particular interest is to employ a regimen where the subject compound is used with an agent for treating alopecia, such as Minoxidil⁷ or Aminexil⁷ (a trademark of L=Oreal), where the dosage employed for the known agent may be the same as in the absence of the subject compound or may be reduced based on the observed experience with the combination. Determining the optimum dosage for the combination can be done in conventional ways using appropriate clinical studies and varying ratios of the two ingredients, which may be in a common formulation or employed as two independent formulations.

The subject compounds may be used in competitive assays or as controls for evaluating other compounds as to their cytostatic or cytotoxic effect or for blocking the androgen receptor. Thus, specific cell lines may be employed where the effect of an agent on the activity of a subject compound may be determined in relation to the survival rate or other indicia of the target cells. Also, in mixtures of cells containing neoplastic androgenic receptor containing cells, the subject compounds can be used to eliminate the neoplastic cells in the presence of normal cells. Thus, in a variety of cultures, where androgenic receptor containing cells may be susceptible to becoming or are tumorous, by maintaining a cytotoxic level of a subject compound in the medium, cells may be selectively killed.

In addition, the radiolabeled compounds may be used for therapeutic and/or diagnostic purposes, depending upon the choice of radiolabel. The radiolabeled compounds may be formulated in accordance with conventional ways using physiologically acceptable components, exemplified by various liquid dispersants, such as deionized water, PBS, DMSO, ethanol, etc. in conjunction with various additives, e.g. non-ionic detergents, dextrose, stabilizers, antibiotics, etc. Normally, the radioactive label will be provided immediately prior to use, so that the radioactive product will be prepared at the site or be shipped to the site of the injection. The formulation will normally be administered by intravenous injection.

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

EXAMPLES

Example 1: 4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-amino-propionyl)aniline. (BP-34)

A pressure reactor was charged with 4-nitro-3-trifluoromethyl-N-[2,3-epoxy-2-methyl propionyl] aniline, BP-33, (10.0 g, 34.46 mmol) and methanol (100 mL). After cooling to - 70°C, ammonia in excess was condensed into the reactor which was sealed and stirred 14 hours. Following evaporation, the crude solid was washed with cold CH₂Cl₂ (50mL). Filtration and drying gave 6.1g BP-34 (58% yield).

Melting point: 142 - 145°C.

Example 2: 4-nitro-3-trifluoromethyl-N-(2'-hydroxy-2'-methyl-3'-N-(heptafluorobutyramido)propionyl) aniline. (BP-521)

BP-34 (247 mg, 0.80 mmol) under nitrogen with CH₂Cl₂ (5 mL), THF (10 mL) and NEt₃ (1.1 mL, 0.80 mmol) was cooled to 0° C and heptafluorobutryl chloride added (120 µL, 0.80 mmol). After cooling at RT the volatiles were removed. CH₂Cl₂ (30 mL) and H₂O (50 mL) were added, the organic layer separated and dried over MgSO₄. The product after silica gel (CHCl₃/acetone) was isolated as a colorless oil (320 mg, 82% yield).

¹H NMR (CDCl₃, 500 MHz): δ 9.27 (s, Ar-NHC(O)); 4.75 (s, C-OH); 3.82 (m, CCH₂, NH).

Example 3: 4-nitro-3-trifluoromethyl-4-N-(2'-hydroxy-2'-methyl-3'-pentadecafluorooctyl amido) -propylamide. (BP-562)

To BP-34 (360mg, 1.17 mmol) was THF (10 mL) and NEt₃ (485 µL, 3.5 mmol) were added. The solution was cooled to 0°C and pentadecyloctanoyl chloride added (295 µL, 1.17 mmol). After reaching RT, the volatiles were removed. After silica gel (CHCl₃/acetone), the product was obtained as a pale yellow solid (689 mg, 84% yield).

Mass spectrum (m/z): 704 (MH⁺); 726 (M+Na⁺). ¹⁹F NMR (470 MHz, CDCl₃): -56.8 ppm, -77.3, -116.3, -118.1, -118.6, -119.1, -119.4, -122.7.

Example 4: 4-nitro-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-N-(heptafluorobutyl)aminopropionyl] aniline. (BP-626)

BP-33 (50 mg, 0.172 mmol) was dissolved in THF (1 mL) and 2,2,3,3,4,4,4-heptafluorobutyl amine (200 mg, 1 mmol), and heated at 90°C for 6 hours. After stripping, the solid after silica gel (CH₂Cl₂/acetone), gave BP-626 as an oil. (61 mg, 72% yield)

mass spectrum (m/z): 590 (MH⁺), 512 (MNa⁺)

Example 5: 2-thioethylheptafluorobutyramide. (BP-532)

Heptafluorobutyryl chloride (11.9g, 51 mmol) was added to a solution of 2-(Striphenylmethylthio) ethylamine (15.58g, 49 mmol) and NEt₃ (5.43g, 54 mmol) in CH₂Cl₂ (50 mL) at 0°C. After 2 hrs. the reaction was quenched and extracted with H₂O (1 x 20 mL), saturated NaHCO₃ (20mL), and saturated NaCl (20 mL). Solvent were evaporated and the residue crystallized from hexane (150 mL) to yield (23.06g (91.3%).

mp: 99 - 104°C

Trifluoroacetic acid (22.16g, 194 mmol) was added to a solution of the product (10.02g, 194 mmol) in CH₂Cl₂ (20 mL). After 5 minutes, triethylsilane (5.65g, 49 mmol) was added. Solvent was evaporated and the solid was purified by silica gel chromatography (CH₂Cl₂) to yield (4.69g, 88.3%).

Example 6: 4-cyano-3-trifluoromethyl-N-[(2'-hydroxy-2'-methyl-3'-S-{2"-heptafluorobutyramido)ethyl}thio}propionyl)aniline. (BP-533)

A solution of BP-532 (1.6 g, 5.9 mmol) in THF (5 mL) was added to a suspension of NaH (0.157g, 6.6 mmol) in THF (2.6 mL) at 0° C. After 30 min, a solution of 4-cyano-3-trifluoromethyl-N-[2,3-epoxy-2-methylpropionyl] aniline (1.58 g, 5.9 mmol) in THF (5 mL) was added at RT. The reaction was quenched with H₂O and extracted with Et₂O (3 x 20 mL). Solvent was evaporated and the residue purified by silica gel chromatography (chloroform/acetone) to yield a white, crystalline solid (2.55 g, 79.9% yield).

Example 7. 4-cyano-3-trifluoromethyl-N-(2'-hydroxy-2'-methyl-3'-S-(2''-heptafluorobutyramido)ethyl) sulphonylpropionyl)aniline. (BP-567 + BP-568)

A solution of sodium metaperiodate (0.18 g, 0.86 mmol) in water (10 mL) was added dropwise to a solution of BP-533 (0.39 g, 0.72 mmol) in MeOH (15 mL) at RT. After stirring for 14 h, the filtered solid was washed with MeOH (15 mL). Volatiles were evaporated in EtOAc (100 mL) and extracted with water (10 mL), 10% aq. sodium sulfite (15 mL) and then saturated NaCl (15 mL). The organic layer was dried over MgSO₄ and solvent was evaporated. The residue was purified by silica gel chromatography (50:50 CHCl₃/acetone) to yield two diastereomers as white, crystalline solids (0.31 g, 78.0%).

Example 8. 4-cyano-3-tri-fluoromethyl-N-[(2'-hydroxy-2'-methyl-3'-S-(2''-heptafluorobutyramido)ethyl)sulfonylpropionyl)aniline. (BP-534)

A solution of MCPBA (0.796 g, 4.6 mmol) in CH₂Cl₂ (100 mL) was added dropwise to BP-533 (1.09 g, 2.01 mmol) in CH₂Cl₂ (100 mL). After stirring for 14 h, the reaction was quenched with 10% aq. sodium sulfite (20 mL), extracted with Na₂CO₃ (2 x 15 mL), and brine (15 mL). Solvent was evaporated and the residue purified by silica gel chromatography (CHCl₃/ acetone) to yield the product as an oil (0.93 g, 79.8%).

Example 9. 4-[2'-5'-dioxo-3',3'-dimethyl-1'-pyrrolidinyl]-2-trifluoromethyl-benzonitrile. (BP-245)

2,2-dimethyl succinic anhydride (34.41 g, 268 mmol) was placed in a flask and melted at 140°C under nitrogen. 5-amino-2-trifluoromethyl benzonitrile (25 g, 134 mmol) was added in portions, followed by methanesulfonic acid (500 µL). After two hours, temperature was reduced to 120°C and EtOAc (200mL) was added. The solution was washed with NaHCO₃ (2 x 50 mL), then saturated NaCl (50 mL). Drying (MgSO₄), filtration, and removal of the solvents left an oil, which was dissolved in toluene (200 mL) at 60° C. After several days, filtration and drying yielded BP-245 (25.7g, 65%) as colorless crystals.

HPLC purity = 99%, melting point: 131-133° C.

Example 10: 4-[2',5'-dioxo-3',3',4'-trimethyl-1'-pyrrolidinyl]-2-trifluoromethyl--benzonitrile. (BP420)

BP-245 (10 g, 34 mmol) was dissolved in DMF (40 mL) and THF (20 mL) in a Schlenk flask and cooled to -78°C under nitrogen. Lithium bis(trimethylsilyl)amide (34 mL, 1 M in THF; 34 mmol) was added over 10 minutes, iodomethane (5.1 g, 35.7 mmol) in THF (20 mL). The reaction was allowed to warm to RT and stirred for 12 hours. The reaction was poured into toluene (400 mL). 1N HCl (200 mL), the layers separated and the toluene layer washed with 50% saturated NaCl (100 mL). Drying (MgSO₄), filtration and solvent removal gave a yellow, crystalline solid, which was purified by silica gel (toluene/acetone) and crystallized from toluene (40 mL) to yield a white, crystalline solid. (2.19 g, 21% yield).

Example 11: 4-[2',5'-dioxo-3',3',4',4'-tetramethyl-1'-pyrrolidinyl]-2-trifluoromethyl--benzonitrile. (BP-424)

BP-245 (5.0 g, 16.9 mmol) was dissolved in dry DMF (22 mL) and cooled to -60° C. Lithium bis(trimethylsilyl) amide (33.8 mL 1 M in THF; 33.8 mmol) was added over 10 minutes, followed by iodomethane (5.025 g, 35.4 mmol) in THF (10 mL). After 6 h at -20° C, mixture was poured into toluene (200 mL) 1 N HCl (100 mL). The layers were separated and the toluene layer washed with saturated NaCl (50 mL). Drying (MgSO₄), filtration and solvent removal gave an oil, which was purified on silica gel (toluene/acetone). Yield of BP-424 = 3.25 g (60%) melting point: 162.5-164° C.

Example 12: 4-[2'-oxo-5'-hydroxy-3',3',4',4'-tetramethyl-1'-pyrrolidinyl]-2-trifluoromethyl-benzonitrile. (BP-511)

BP-424 (100 mg, 0.31 mmol) was dissolved in methanol (2 mL) and 1 N HCl (100 µL). At 15° C, solid sodium borohydride (58 mg, 1.54 mmol) was added over 2 minutes. After 14 h at RT, methanol was removed, and the product partitioned between EtOAc (20 mL) and 10 % NaCl (25 mL). The layers were separated, the organic layer washed with saturated NaCl (25 mL) and dried (MgSO₄), and evaporated to give a white solid (109 mg) which was further purified by crystallization from CH₂Cl₂. (88 mg, 87% yield)

Melting point: -195-197°C. Mass spectrum (m/z): 325 (MH⁺) MW = 326.32

Example 13: 4-(2'-oxo-5'-heptafluorobutyloxy-3',3',4',4'-tetramethyl-1'pyrrolidinyl)-2-trifluoromethyl benzonitrile. (BP-569)

BP-511 (100 mg, 0.036 mmol) was suspended in 2,2,3,3,4,4,4-heptafluorobutanol (1 mL) and methanesulfonic acid (100 μ L) and was stirred at RT for 6 hours. The solution was poured into 0.1 M K_2HPO_4 (pH 7.0, 15 mL) and EtOAc (25 mL). The organic layer was washed with brine (2 x 10 mL) and dried ($MgSO_4$). Stripping and silica gel chromatography (CCl_4 /acetone) gave a white solid (53 mg, 34% yield).

Mass spectrum (m/z): 509 (MH^+)

Example 14: 4-[3'-(4"-N-t-butoxycarbonyl)-aminobutyl]-4',4'-dimethyl-5'-imino-2'thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-380)

4-cyano-3-trifluoromethyl phenylisothiocyanate (2.3 g, 10 mmol) was dissolved in THF (15 mL), and NEt_3 (1.43 mL, 10.3 mmol) then added to crude 2-(1',4'-butylamino-N-tbutoxy-carbonyl)-2-cyanopropane (2.6 g, 10.2 mmol) in THF (10 mL). After 1.5 hr, the volatiles were removed in vacuo. Silica gel column ($CHCl_3$ /acetone) gave a yellow solid (3.6 g) 94% pure by HPLC.

1H NMR (500 MHz, $CDCl_3$): δ 3.20 (m, 2H, $CH_2NHC(O)$); 3.68 (m, 2H, $CH_2NC(S)$).

Example 15: 4-[3'-(4"-aminobutyl)-4',4'-dimethyl-5'-imino-2'thio-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-381)

BP-380 (21.0 g, 44 mmol) was dissolved in MeOH (80 mL). 4 N HCl (40 mL, 160 mmol) and methanol (40 mL) were added. After reflux for 1.5 hr and evaporated. The product was filtered from an EtOH slurry, washed with cold EtOH (50 mL) and dried under vacuum to give a colorless solid (15.8 g, 88.5% yield).

1H NMR ($DMSO-d_6$, 500 MHz): δ 3.72 (m, 2H NCH_2CH_2); 2.82 (m, 2H, $CH_2CH_2NH_3$); 1.55 (s, 6H, CCH_3).

Example 16: 4-[3'-(4"-heptafluorobutyramidobutyl)-4',4'-dimethyl-5'oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-443)

BP-381 (15.8 g, 37.6 mmol) was placed in a flask with CH_2Cl_2 (200 mL) and NEt_3 (23 mL, 165 mmol). Heptafluorobutyryl chloride was added (6.2 mL, 41.3 mmol). After stirring for 6 h at RT and everything followed by silica gel (CHCl_3 /acetone). An oil (8.9 g) resulted (41% Yield).

- 5 ^{19}F NMR (CDCl_3): -58.5 ppm (ArCF_3); -77.1 (CF_2CF_3); -117.2 (C(O)CF_3); -123.4 ($\text{CF}_2\text{CF}_2\text{CF}_3$).
 ^{13}C NMR (CDCl_3 127 MHz): 157.8 ppm 175.13, 178.55.

Example 17: 4-[3'-((4''-heptafluorobutylamidoethyl)butyl)-4',4'-dimethyl-5'-imino-2'--thioxo-1'-imidazolidinyl]-2-trifluoromethyl benzonitrile. (BP-444)

- 10 BP-138 (340 mg, 0.95 mmol; acc. to example 7) was dissolved in CH_2Cl_2 (5 mL) and NEt_3 (0.397 mL, 2.85 mmol). Heptafluorobutyryl chloride was added (0.142 mL, 0.95 mmol). After 30 minutes at RT, the volatiles were removed. Silica gel (CHCl_3 /acetone) gave a colorless solid (280 mg) (5 % Yield).

- 15 ^{19}F NMR (470 MHz, CDCl_3): -58.6 ppm, -77.0, -117.0, -123.3.

Example 18: N-(4-cyano-3-trifluoromethyl-phenyl)-N'-heptafluorobutyl) thiourea. (BP-628)

- 20 4-cyano-3-trifluoromethyl phenylisothiocyanate (2.28g, 10 mmol) was dissolved in THF (15mL), and cooled to 5°C. 2,2,3,3,4,4-heptafluorobutyl amine (209 mg, 10.5 mmol) was added after stirring for 1 h, with EtOAc (60 mL) and 1 N HCl (25 mL) were added. The organic layer was washed with saturated NaCl (15 mL) and dried (MgSO_4). Silica gel chromatography (CH_2Cl_2 /acetone), gave a white solid (90% yield).

- 25 *Example 19: 4-nitro-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-{N'-(methyl)-N'-(3''-phenyl-3''-(p-trifluoromethyl phenyl))propyl}amino}aniline. (BP-657)*

BP-33 (77 mg, 0.264 mmol) and fluoxetine (68 mg, 0.22 mmol) were dissolved in p-dioxane (3 mL) and the solution heated for 6 hours at 95°C. The solvent was removed and the product purified on silica gel (CH_2Cl_2 /MeOH/ NEt_3). Yield = 64 mg (48% Yield).

Example 20: -hydroxy-3-((2-hydroxy-2-(N-(4-nitro-3-(trifluoromethyl)phenyl)carbamoyl)propyl) amino)-2-methyl-N-(4-nitro-3-(trifluoromethyl)phenyl)propanamide. (BP-673)

BP-33 (1.0g, 34 mmol) was dissolved in methanol (40 mL). NH_4OH (30%, 4 mL) was added and the reaction stirred at room temperature for 24 hs. The volatiles were removed and the crude solid chased with methanol (2 x 10 mL). The product was collected as a precipitate from methylene chloride and further purified using column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ gradient) to give a yellow solid. Yield of BP-673 = 490 mg (48%).

Mass Spectrum (m/z): MH^+ 598.

Example 21: 2-hydroxy-3-((2-(2-(2-hydroxy-2-(N-(4-nitro-3-(trifluoromethyl)phenyl)carbamoyl) propyl) amino) ethoxy) ethoxy)ethyl)amino)-2-methyl-N-(4-nitro-3(trifluoromethyl) phenyl)propanamide. (BP-676).

BP-33 (500 mg, 1.72 mmol) was placed in flask with stir bar. Dioxane was added. In a separate flask, dissolved diamine (Hunstman XTJ-504) (127 mg, 0.86 mmol) in Dioxane (4 mL). This was added to the former and the resulting solution was stirred and heated at 90° C for 5 hr. The oil bath was removed and the reaction stirred for 9 hr. at room temperature. The volatiles were removed and chloroform added (10 mL), to give a colorless precipitate, which was collected and dried to give the product as a colorless solid. Yield of BP-676 = 290 mg (46%).

Mass Spectrum (m/z): MH^+ = 729

Example 22: N-(4-chlorophenyl)-3-((2-(N-(4-chlorophenyl)carbamoyl)-2--hydroxypropyl)amino)-2-hydroxy-2-methylpropanamide. (BP-708)

BP-706 (3.0 g, 14.2 mmol) was dissolved in CH_3OH in flask and stir bar. NH_4OH (12 mL) was added turning solution into yellow liquid. After stirring two days, the volatiles were removed and the crude product chased with MeOH (2 x 120 mL). The product was purified using column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ gradient) and isolated to produce white crystals. Yield of BP-708 = 2.56 g (41%).

Mass Spectrum (m/z): $MH^+ = 440$

mp. 76-78°C

Example 23: 3-((((4-bromophenyl)amino)thioxomethyl)amino)-2-hydroxy-2-methyl-

N-(4-nitro-3-(trifluoromethyl)phenyl)propanamide. (BP-668)

BP-34 (2.0g, 6.5 mmol) was dissolved in anhydrous THF (30 mL) under $N_2(g)$. NEt_3 was added (100 μ L). In a separate flask under $N_2(g)$, 4-bromophenylisothiocyanate was similarly added to the former mixture. After stirring for 1h, the volatiles were removed and the crude product purified via silica gel column chromatography ($CHCl_3$ /acetone gradient) to give the product as a yellow solid (m.p. 192-195°C) in 67% yield.

Mass Spectrum (m/z): $MH^+ = 521, 523$

Example 24: 3-((((cyclohexylmethyl)amino)thioxomethyl)amino)-2-hydroxy-2-

methyl-N(4-nitro-3-(trifluoromethyl)phenyl)propanamide. (BP-743)

BP-34 (2.0g, 6.5mmol) was dissolved in anhydrous THF (30 mL) under $N_2(g)$. NEt_3 was added (2.7 mL) and then followed by cyclohexylmethylisothiocyanate (1.0g, 6.4 mmol). After stirring for 3h, the volatiles were removed and product purified via silica gel column chromatography (CH_2Cl_2 : acetone gradient) to give a yellow solid (m.p. 77-81°C) in 84% yield.

Mass Spectrum (m/z): $MH^+ = 463$; $MNa^+ = 485$.

Example 25: 4-[2',5'-dioxo-3',3',4'-trimethyl-4'-propynyl-1'-pyrrolidinyl]-2-

trifluoromethyl-benzonitrile. (BP-535)

BP-420 (1.71 g, 5.5 mmol) was placed in a flask. After cooling to -50°C, lithium bis(trimethylsilyl)amide (5.55 mL, 1 M in THF; 5.55 mmol) was added, followed by propargyl bromide (0.69 g, 58 mmol). The reaction was held at 0°C overnight after which it was poured into 1 N HCl (30 mL) and extracted with EtOAc. The organic layer was washed with 50% saturated NaCl (100 mL). Drying ($MgSO_4$), filtration and solvent removal gave a solid, which was purified on silica gel (toluene/acetone). The product was re-crystallized from toluene (1.05 g, 55% yield).

Example 26: 2-(trifluoromethyl)-4-(3,3,4-trimethyl-2,5-dioxo-4-(6,7,7-trifluorohept-6-en-2-ynyl)cyclopentyl)benzenecarbonitrile. (BP-751)

BP-535 (120mg, 0.34 mmol) is dissolved in anhydrous THF (10 mL) and the solution cooled to -78°C. $\text{KN}(\text{SiMe}_3)_2$ (344 μL , 1 M in toluene) is added, followed by $\text{BrCH}_2\text{CH}_2\text{CF}=\text{CF}_2$ (65mg, 0.34 mmol). The solution is allowed to warm to RT, is quenched with 1 N HCl and extracted with EtOAc. The layers are separated and the organic layer dried (MgSO_4), filtered and concentrated to give the crude product, which is purified via column chromatography to give the product as a colorless solid.

Example 27: 4-cyano-3-trifluoromethyl-N-(2'-hydroxy-2'-methyl-3'-N-(heptafluorobutyramido)propionyl) aniline (BP-713)

BP-646 (the cyano analog of BP-34) (1.121 g, 3.89 mmol) was dissolved in dry CH_2Cl_2 and NEt_3 (1.6 mL) was added. Heptafluorobutyryl chloride was added (558 μL , 4.28 mmol). After 3h, volatiles were removed and the product purified by silica gel chromatography (CH_2Cl_2 /acetone) to give a colorless solid (1.03 g, 55% yield)

Mass spectrum (m/z): 482(MH^+). Melting point 142-144EC

Example 28: N-(3-trifluoromethyl-4-cyanophenyl), N=-propyl thiourea (BP-735)

4-Cyano-3-trifluoromethylphenylisothiocyanate (1 g., 4.39 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0EC. n-Propylamine was added slowly and the ice bath removed. After stirring at RT for 16 h, volatiles were removed and the product was crystallized from toluene to give off-white plates (1.02 g, 77% yield).

Example 29: 2-hydroxy-3-(((4'-iodophenyl)amino)carbonylamino)-2-methyl-N-(4"-nitro-3"-trifluoromethyl)phenyl)propanamide (BP-754)

BP-34 (2.35 g., 7.66 mmol) was dissolved in anhydrous THF (25 mL). In a separate flask, p-iodophenylisocyanate (2.0 g., 8.16 mmol) was dissolved in anhydrous THF (10 mL). NEt_3 (3.2 mL) was added to the first solution, followed by addition of the isocyanate solution. After 2 h, the

volatiles were removed and the crude product washed with CH₂Cl₂ (2 x 50 mL) and the resulting product collected as a pale yellow solid (4.0 g., 95% yield).

Example 30: 4-[3'-trans-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thiooxo-1'-imidazolidinyl]-2-trifluoromethylbenzonitrile (BP-305); 4-[3'-cis-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thiooxo-1'-imidazolidinyl]-2-trifluoromethylbenzonitrile (BP-305)

BP-199 (4-[4',4'-dimethyl-3-propargyl-5'-oxo-2'-thiooxo-1'-imidazolidinyl]-2-trifluoromethylbenzonitrile; see WO97/00071) was dissolved in dry toluene (100 mL) under N₂. Bu₃SnH (1.12 mL) and AIBN (68.5 mg) were added and the reaction mixture heated to reflux. After stirring for 3 h at reflux, the reaction was allowed to cool to rt and the volatiles removed under vacuum. The crude product was purified by column chromatography (SiO₂, eluent CHCl₃) isolated as a pale oil (1.67 g). Purity 95.3% HPLC.

BP-237 (80:20 E/Z isomers, 370 mg) was dissolved in CHCl₃ (5 mL) and cooled to 0EC. In a separate flask, I₂ (146 mg) was dissolved in CHCl₃ (15 mL) and added to the solution of BP-237. After 2 h at rt, the volatiles were removed and the product mixture purified using silica chromatography (gradient CHCl₃/acetone). BP-305 (trans isomer) was isolated as a white crystalline solid 200 mg, m.p. 137-139EC. Purity was 96.4% (contaminated with 1.2% of BP-307 (HPLC)). Pure BP-307 was obtained by further use of column chromatography (70 mg, m.p. 146-7EC, purity 99.2%:HPLC)

Example 31: 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-(propargyloxypropionyl)] aniline (BP-632)

To a solution of propargyl alcohol (2.59 mL, 44.5 mmole) cooled to -78EC was added dropwise a solution of methyl lithium in diethyl ether (27.8 mL, 1.6M). After 30 min a solution of 4-cyano-3-trifluoromethyl-N-[2,3-epoxy-2-methylpropionyl]aniline (4.0 g, 14.8 mmole; prepared according to the general method in EP 0 100 172) in THF (40 mL) was added. The solution was allowed to reach rt, stirred 20 h and the volatiles removed. The residue was partitioned between THF/sat. aq. NaCl (50 mL/50 mL), the organic layer concentrated under reduced pressure to an oil and purified by silica chromatography (CHCl₃/acetone) to yield 4.27 g (88%) BP-632.

Example 32: 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-(¹²⁵I)iodo-trans-2''-propenyloxy]propionyl aniline (BP-636); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-(¹²⁵I)iodo-cis-2''-propenyloxy]propionyl aniline (BP-637);
 5 *4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[gem- di-3''-(¹²⁵I)iodo-2''-propenyloxy]propionyl aniline (BP-638)*

A. 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-tributylstannyl-trans-2''-propenyloxy]propionyl aniline (BP-633); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-tributylstannyl-cis-2''-propenyloxy]propionyl aniline (BP-634); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[gem- di-tributylstannyl-2''-propenyloxy]propionyl aniline (BP-635)

To a solution of BP-632 (2.60 g, 8.0 mmole) in toluene (30 mL) was added BuSnH (3.21 mL, 12.0 mmole) and AIBN (1.39 g, 12.0 mmole). The solution was refluxed for 20h, the volatiles removed and the crude product purified on silica chromatography (CHCl₃/acetone) to yield 4.07 g (89%) of
 15 an 8:1:1 mixture of trans, cis and gem isomers (BP-633, -634, -635)

B. The mixture prepared above is dissolved in a small amount of DMF. Radioiodination is accomplished using Na[¹²³I], Na[¹²⁵I] or Na[¹³¹I] by known methods. (See Hunter and Greenwood, Nature (1962) 194:495-6)

Example 33: 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-(¹²⁵I)iodo-trans-2''-propenylthio]propionyl aniline (BP-552); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3''-(¹²⁵I)iodo-cis-2''-propenylthio]propionyl aniline (BP-553);
 25 *4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[gem- di-3''-(¹²⁵I)iodo-2''-propenylthio]propionyl aniline (BP-554)*

A. A solution of propargylthiol (100 mL, 0.13M in THF/CH₂Cl₂; prepared according to Castro, J. et al., Synthesis 1977, 518) was added to a suspension of NaH (0.52 g, 13.0 mmole, 60% in oil) in THF (25 mL) at -78°C and stirred for 1 h. To this cold solution was added a solution of 4-cyano-3-trifluoromethyl-N-[2,3-epoxy-2-methylpropionyl] aniline (3.51 g, 13.0 mmole; prepared according
 30 to EP 0 100 172 general method) in THF (20 mL) and stirred 1 h at -78°C. The solution was allowed to reach rt, stirred 1 h and the volatiles removed. The residue was partitioned between

$\text{CHCl}_3/\text{H}_2\text{O}$ (200 mL/200 mL), the organic layer concentrated to an oil under reduced pressure and purified by silica chromatography (CH_2Cl_2) to yield 1.13 g (25%) BP-548

B. 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3"-tributylstannyl-trans-2"-propenylthio]propionyl aniline (BP-549); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[3"-tributylstannyl-cis-2"-propenylthio]propionyl aniline (BP-550); 4-cyano-3-trifluoromethyl-N-[2'-hydroxy-2'-methyl-3'-[gem-2"-di-3"-tributylstannyl-2"-propenylthio]propionyl aniline (BP-551)

BP-548 (1.03 g, 30 mmole) was dissolved in 1,4-dioxane (15 mL) and toluene (30 mL). Bu_3SnH (1.21 mL, 4.5 mmole) and AIBN (0.52 g, 4.5 mmole) were added and the reaction mixture heated to reflux for 12 h. The volatiles were removed and the crude product was purified on silica chromatography (CHCl_3) to yield 0.78 g (44%) of a 5:3:2 mixture of the gem, cis and trans isomers. (BP-551, -550, and -549, respectively).

C. The mixture of BP-549, -550 and -551 prepared above is dissolved in a small amount of DMF. Radioiodination is accomplished using $\text{Na}[^{123}\text{I}]\text{I}$, $\text{Na}[^{125}\text{I}]\text{I}$ or $\text{Na}[^{131}\text{I}]\text{I}$ by known methods. (See Hunter and Greenwood, Nature (1962) 194:495-6).

Compounds were tested for stability in human serum at 38°C. They were dissolved in isopropanol/ H_2O (95:5), mixed with human serum to a concentration of 0.5 mg/mL, and incubated at 38°C. Serum aliquots were extracted with ethyl acetate and analyzed by HPLC. In an accelerated stability study of the compounds BP-521, BP-668 and BP-673, formulated in isopropanol/ H_2O (95:5) and incubated at 50°C, no change was observed via HPLC up to six days.

Table 1

Percent of the intact compound remaining in human serum at 38°C after incubation.

Compound	6h	24h	48h	6d
BP-521	97.5	90.0	84.0	60.0
BP-668	-	100	100	100
BP-673	-	100	100	100

It can be seen that the compound containing aliphatic perfluorocarbon has a limited stability resulting from hydrolysis of the perfluoroamide, leaving the free amine, BP-34 (Example 1) and the perfluorocarbon moiety. Compounds BP-673 (a dimeric species) and BP-668 have nevertheless proved stable.

Compounds which were found sufficiently stable were dissolved in EtOH/DMSO and incubated with human prostate cancer cells LNCaP, which contain AR with a minor mutation. After 72 hours, an XXT assay (Scudievo, et al., Cancer Research, 48:4827 (1988)) indicating cell viability was carried out. Table 2 shows the lowest drug concentrations needed to abolish 50% of the cellular viability.

Table 2
Effect on cell viability

Compound:	Molar Concentration:
Bicalutamide	7.0 H 10 ⁻⁵
Hydroxyflutamide	5.0 H 10 ⁻⁵
BP-34	<1 H 10 ⁻⁴
BP-443	5.5 H 10 ⁻⁶
BP-463	5.5 H 10 ⁻⁵
BP-483	6.25 H 10 ⁻⁶
BP-521	5.6 H 10 ⁻⁶
BP-546	4 H 10 ⁻⁶
BP-668	1.5 H 10 ⁻⁵
BP-673	2.7 H 10 ⁻⁵
BP-676	1.4 H 10 ⁻⁵
BP-713	1 H 10 ⁻⁵

The interaction of the compounds with AR was studied by incubation with LNCaP cells, subsequent cell lysis and the standard Western Blot assay. Table 3 shows percent of remaining AR contained in the lysate following incubation of the cells with test compounds for 48 hours.

Table 3

Percent of the androgen receptor remaining in human prostate cancer cells, LNCaP,
by Western Blot.

Compound:	@ 3 μ Molar conc.:	@ 10 μ Molar conc.:
BP-34	97	98
BP-52	38	0
BP-668	73	0
BP-673	74	3
BP-676	64	20
BP-713	50	3
BP-735	45	1
BP-754	28	14
Bicalutamide	97	89
Hydroxyflutamide	98	94

5 It can be seen that not all compounds which showed strong inhibition of LNCaP cells, by
XXT assay, were also correspondingly active in suppressing the AR. While the control
antiandrogens, i.e. hydroxyflutamide and bicalutamide, have not shown any significant effect on the
AR, important suppression was found at 3 μ M concentration with compounds BP-521, BP-673, BP-
668, BP-713 and BP-735. These compounds practically eliminated the AR at 10 μ M concentration.

10 The free amine, BP-34, a product of the composition of BP-521, had no effect on the AR,
nor on the LNCaP cells.

BP-521 bioavailability results are shown in Table 4.

Table 4
Bioavailability of BP-521

Species	Applic./dose in mg/kg bw	$\mu\text{g/ml}$ blood at hrs.:						Cumulative mg/total blood volume and % dose	
		0.5	1.0	1.5	2.5	7.0	24		
Rabbit ~ 3kg	oral, 100	1.5	1.7	2.6	1.5	1.0	1.0	3.0 μg	1.50%
Rabbit ~ 3 kg	i.p., 150	1.9	3.2	1.9	1.5	3.0	2.2	11.6 μg	2.8%
Rabbit ~ 3 kg	skin 20 cm^2 100 mg/d, 10 d	0	0	0	0	0	0	0	0
Rat ~ 140 g	i.m., 75	0.7	4.7	2.2	-	-	1.0	2.1 μg	2.9%

It can be seen that only a fraction of the dose is systemically available upon oral, i.p. or i.m. application, that the peak serum levels in the oral test was 0.0052% of the injected dose, as compared to the 0.03% reported for bicalutamide (Cockshott ID, et al. *Eur Urol.* 1990, Vol 18, Suppl. 3: 10-17). The bioavailability of BP-521 from the subcutaneous, muscle and interperitoneal spaces was also low.

When intact rats were given 10 times subcutaneously 100mg/kg of BP-521, the average weight of their prostate and seminal vesicles was reduced by about 46%. On the other hand, 0.1mg/kg dose of BP-521 or BP-668 in castrated rats supplemented with testosterone propionate did not reduce the secondary sex organs' weight, while 0.5mg/kg of bicalutamide did, by about 20%. (The dose of 0.1mg/kg approximates the expected topical daily dose for humans).

Topical absorption was studied in rabbits who were treated 2x daily with 0.5 mL of a 10% solution of BP-521 in 50/50 PEG 400/EtOH over a shaved skin area of 20 cm^2 . No absorption was found by HPLC with standard calibrated sensitivity of detection of 5 nanograms.

Systemic toxicity was orientationally evaluated by i.p. injection every 2nd day in mice. BP-521, 200mg/kg bw was given 5 times, without mortality or morbidity, while morbidity but no mortality was seen at 350mg/kg bw. For BP-34, the corresponding values were 150mg kg bw and 300mg/kg bw.

5 In an orientational test on three male volunteers, 1% solution of BP-521 in ethanol, 0.5 mL applied twice daily on the affected scalp, effectively arrested incipient androgenic alopecia of the forehead line and after 8 weeks, induced copious growth of vellum hair.

10 It can be concluded that BP-521, due to the low systemic toxicity and lack of cutaneous absorption and the generally low bioavailability is suitable for treatment of skin disorders where slow biodegradability is an advantage: the resulting free amine, BP-34, has no antiandrogenic activity, and the other decomposition product, perfluorobutyric acid, was shown to have low toxicity (Takagi A, et al. *Cancer Letters*. 1991, 57: 55-60).

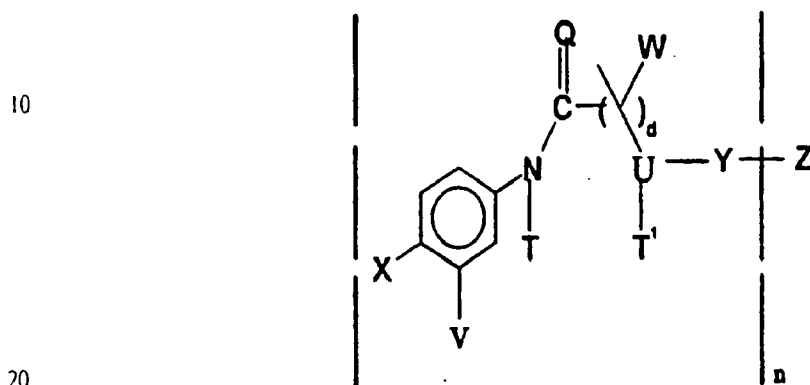
15 Test compounds containing non-radioactive iodine (BP-554, -636 and -305 were shown to interact with AR as compared to controls. These compounds were formulated using a standard medium comprising ethanol, DMSO, Tween and dextrose in water and were injected intravenously into 300 g male rats. After 4 h the rats were sacrificed and the amount of the test element determined in various organs and blood relative to the prostate levels. There was a substantial accumulation in the prostate vis-a-vis the other tissues which were analyzed. As described in U.S. Patent no. 5,656,651, the subject compounds can be used for whole body scanning to depict prostate cancer and metastases.

20 It is evident from the above results that compounds are provided which are effective with indications associated with the androgen receptor, such as androgen dependent tumors, and skin androgen mediated disorders, such as acne, hirsutism and androgenetic alopecia. In addition to having cytotoxic and cytostatic activity, some of the compounds demonstrate androgen receptor suppression. For topical treatment, compounds are provided which have low resorption.

25 Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims. All references cited herein are incorporated herein by reference, as if set forth in their entirety.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

X is nitro, cyano or halogen;

V is CF₃, halogen or H;

25 W is OH when T is H and is methyl when T and T' are taken together to form a C=Z bridge;

U is N when T and T' are taken together to form a C=Z bridge or is taken together with T' to form a bond or O, S or N;

n is 1 or 2 and d is 0 or 1;

30 when d is 0, T and T' are hydrogen;

when d is 1, then:

when n is 1 or when d is 0, Y is a bond or linking group of from 1 to 10 carbon atoms and from 0 to 6, with from 0 to 4 heteroatoms in the chain, where the heteroatoms are N, O, or S; and

35 Z, when other than taken together with Y, is an aliphatic group of from 1 to 6 carbon atoms, which may be saturated or unsaturated, a polyfluoroacylamido group of from 2 to 8, usually 2 to 6, more usually 3 to 5 carbon atoms and having at least 2 fluorines and not more than 2m-1 fluorines, wherein m is the number of carbon atoms, or haloanilino, where halo is of atomic number 9 to 80; and radiolabeled derivatives thereof.

2. A compound according to Claim 1, wherein n is 1.

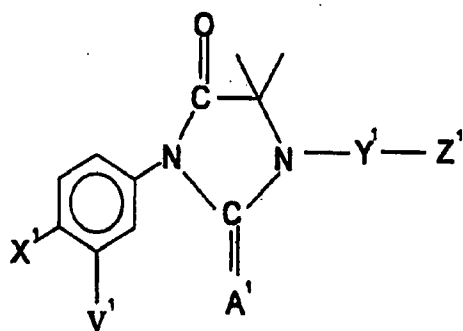
3. A compound according to Claim 2, wherein Z is perfluoroacylamido

4. A compound according to Claim 1, wherein n is 2.

5. A compound according to Claim 4, wherein T and T¹ are H and Y and Z are taken together to define a linking group of a total of from 2 to 8 carbon atoms and O, S and N heteroatoms.

6. A compound according to Claim 1, wherein Z is radiolabeled with an iodine radioisotope.

7. A compound of the formula:



wherein:

X¹ is nitro or cyano;

V¹ is CF₃;

A¹ is chalcogen;

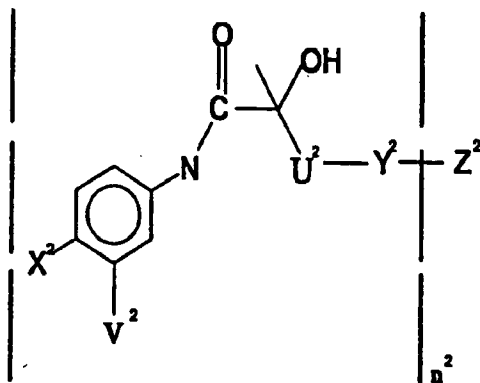
Y¹ is alkylene of from 2 to 8 carbon atoms;

Z¹ is a polyfluoroacylamido of from 2 to 8 and having at least 2m-2 fluoro groups, wherein m is the number of carbon atoms, or substituted arylamino of from 6 to 10 carbon atoms, particularly, and halogen of atomic number from 9 to 80; and

radiolabeled derivatives thereof.

8. A compound according to Claim 7, wherein Z is a polyfluoroacylamido group and A¹ is sulfur.

9. A compound of the formula:



wherein:

X² is nitro or cyano;

V² is CF₃;

n² is 1 or 2;

U² is a bond, N or chalcogen;

when n is 1, Y² is a bond or linking group of a total of from 1 to 6 atoms, which are C, N, O, and S; with the proviso that when U² is a bond, Y² is also a bond; and

Z² is polyfluoroacylamido of from 2 to 6 carbon atoms and at least 2m - 2 fluorine atoms, wherein m is the number of carbon atoms, an aliphatic group of from 1 to 6 carbon atoms substituted with a radioisotope or haloanilino, where halo is of atomic number 9 to 80; when n is 2, Y² and Z² are taken together to form a linking group of a total of 1 to 10 C, N, O, and S atoms.

10. A compound according to Claim 9 of the formula 4-nitro-3-trifluoromethyl-N-({2'-hydroxy-2'-methyl-3'-N-heptafluorobutyramido}propionyl)aniline.

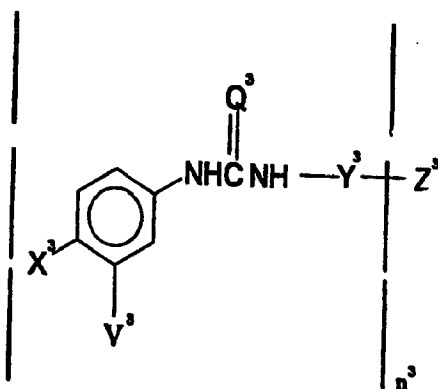
11. A compound according to Claim 9 of the formula 3-(((4'-bromophenyl)amino)thiono)amino)-2-hydroxy-2-methyl-N-(4"-nitro-3"-trifluoromethyl)phenyl)propionamide.

12. A compound according to Claim 9 of the formula N,N-bis-(3,3'-di{N=3"-trifluoromethyl-4"-nitrophenyl}-2"-hydroxy-2"-methylpropionamide)amine.

13. A compound according to Claim 9 of the formula N-(3'-trifluoromethyl-4'-cyano)2-hydroxy, 2-methyl-3-perfluorobutyramidopropionamide.

14. A compound according to Claim 9, wherein Z^2 is an aliphatic group substituted with an iodine radioisotope.

15. A compound of the formula:



wherein:

X^3 is nitro or cyano;

V^3 is CF_3 ;

n^3 is 1 or 2;

Q^3 is chalcogen;

when n is 1, Y^3 is a bond or linking group of a total of from 1 to 6 atoms, which are C, N, O, and S; and

Z^3 is alkyl of from 1 to 6 carbon atoms, polyfluoroacylamido of from 2 to 6 carbon atoms and at least $2m - 2$ fluorine atoms, wherein m is the number of carbon atoms, or haloanilino, where halo is of atomic number from 9 to 80; when n is 2, Y^3 and Z^3 are taken together to form a linking group of a total of 1 to 10 C, N, O, and S atoms.

16. A compound according to Claim 15 of the formula N-(3-trifluoromethyl-4-cyanophenyl), N=-propyl thiourea.

17. A method of treating an indication dependent upon activation of the androgen receptor, said method comprising:
administering an effective amount to inhibit said activation of a compound according to Claim 1.

18. A method according to Claim 17, wherein said indication is a hyper-androgenic skin syndrome and said administering is topical.

19. A method according to Claim 17, wherein said indication is cancer and said administering is systemic.

20. A pharmaceutical formulation comprising a compound according to Claim 1 and a pharmacologically acceptable carrier.

21. A method of treating alopecia, said method comprising:
treating a host suffering from alopecia in a pharmacologically effective amount with a combination of a compound according to Claim 1 and a second agent for treating alopecia, whereby said alopecia is alleviated.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 June 2000 (29.06.2000)

PCT

(10) International Publication Number
WO 00/037430 A3

(51) International Patent Classification⁷: **C07C 237/04**,
A61K 31/16, 31/40, 31/415, C07C 237/22, 323/60,
317/48, C07D 207/40, 207/26, 233/88, 233/86, C07C
235/22, 335/16, 335/08, 255/56, 255/60, 275/30, C07D
207/36, C07M 5/00, A61P 5/00

Terrace, San Diego, CA 92103 (US). **CAMPION, Brian**;
959 North Vulcan Avenue, Leucadia, CA 92024 (US).
BROWN, Jason, W.; 4950 Santa Cruz Avenue, San
Diego, CA 92067 (US).

(21) International Application Number: PCT/US99/26862

(74) Agent: **RAE-VENTER, Barbara**; Rae-Venter Law
Group, P.C., P.O. Box 60039, Palo Alto, CA 94306-0039
(US).

(22) International Filing Date:

12 November 1999 (12.11.1999)

(81) Designated States (*national*): AU, CZ, HU, IL, JP, NO,
PL, SK, ZA.

(25) Filing Language: English

(84) Designated States (*regional*): European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE).

(26) Publication Language: English

(30) Priority Data:

09/215,351 18 December 1998 (18.12.1998) US

Published:

— with international search report

(71) Applicant: **BIOPHYSICA, INC.** [US/US]; 3333 North
Torrey Pines Court #100, La Jolla, CA 92037 (US).

(88) Date of publication of the international search report:
17 April 2003

(72) Inventors: **SOVAK, Milos**; 3333 North Torrey Pines
Court #100, La Jolla, CA 92037 (US). **SELIGSON,**
Allen, L.; 1770 Deavers Drive, San Marcos, CA 92061
(US). **DOUGLAS, James, Gordon, III**; 4066 Moratalla

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 00/037430 A3

(54) Title: USE OF ANDROGEN RECEPTOR SUPPRESSORS

(57) Abstract: Substituted phenylalanines are provided comprising an hydantoin, urea or 2-hydroxyl, 2-methylpropionyl group, dimers thereof and alkyl, polyfluoroamido and haloaryl amino derivatives thereof, as well as radiolabeled derivatives thereof. The compounds bind specifically to the androgen receptor and find use in indication associated with the androgen receptor, such as cell hyperplasia dependent on androgens, hirsutism, acne and androgenetic alopecia.

INTERNATIONAL SEARCH REPORT

Internatl Application No

PCT/US 99/26862

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C237/04 A61K31/16 A61K31/40 A61K31/415 C07C237/22
C07C323/60 C07C317/48 C07D207/40 C07D207/26 C07D233/88
C07D233/86 C07C335/22 C07C335/16 C07C335/08 C07C255/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 411 981 A (GAILLARD-KELLY M ET AL) 2 May 1995 (1995-05-02) claims; examples	7,8
A	US 5 750 553 A (CLAUSSNER ANDRE ET AL) 12 May 1998 (1998-05-12) examples 13-15	7,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

31 March 2000

Date of mailing of the international search report

22/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

PAUWELS, G

INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/US 99/26862

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C255/60 C07C275/30 C07D207/36 C07M5/00 A61P5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

31 March 2000

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

PAUWELS, G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/26862

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-19, 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1 to 6, 17 to 21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

7,8

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 to 6, 17 to 21

The present claim 1 contains so many options, variables, possible permutations and provisos especially with respect to the meanings of n and d and the consequences thereof that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of claims 1 to 6 impossible. Moreover, the meaning of Q, the substituent on N, when U and T1 taken together are N and the meaning Y-Z taken together, has not been defined.

The above obscurities are not solved by when reading the claims in the light of the description pages 5, 6 and the examples. Especially the passage on page 5, lines 36 to 38 is still unclear and many examples seem not to be covered by neither the claims nor the general description on pages 5 and 6. Therefore it is impossible to determine the matter for which protection is sought. Consequently only claims 7 to 19 have been considered for drawing up this search report.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 7,8

1-substituted phenyl, 2-(thi)oxo 3-substituted 5-oxo
4,4-dimethyl imidazoles according to claim 7 and their use.

2. Claims: 9-14

N-substituted phenyl, 2-hydroxy, 2 substituted propionamides
according to claim 9 and their use.

3. Claims: 15, 16

N-substituted phenyl, N' substituted (thio)-urea according
to claim 15 and their use.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US 99/26862

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5411981 A	02-05-1995	FR 2671348 A	10-07-1992
		FR 2693461 A	14-01-1994
		US 5627201 A	06-05-1997
		US RE35956 E	10-11-1998
		AT 140218 T	15-07-1996
		AU 648376 B	21-04-1994
		AU 1010692 A	16-07-1992
		CA 2059052 A	10-07-1992
		CN 1063102 A, B	29-07-1992
		DE 69212007 D	14-08-1996
		DE 69212007 T	09-01-1997
		DK 494819 T	12-08-1996
		EP 0494819 A	15-07-1992
		ES 2089425 T	01-10-1996
		GR 3020510 T	31-10-1996
		HU 60250 A	28-08-1992
		HU 9500325 A	28-09-1995
		IE 76143 B	08-10-1997
		JP 4308579 A	30-10-1992
		RU 2076101 C	27-03-1997
		ZA 9200090 A	31-03-1993
		AU 3987693 A	13-01-1994
		CA 2097248 A	09-01-1994
		CN 1081182 A, B	26-01-1994
		EP 0580459 A	26-01-1994
		HU 64527 A	28-01-1994
		JP 6073017 A	15-03-1994
		RU 2116298 C	27-07-1998
		ZA 9303786 A	30-05-1994
US 5750553 A	12-05-1998	FR 2715402 A	28-07-1995
		FR 2724169 A	08-03-1996
		AU 687152 B	19-02-1998
		AU 1457395 A	01-08-1995
		BR 9506457 A	07-10-1997
		CA 2180379 A	13-07-1995
		CN 1141631 A	29-01-1997
		EP 0738263 A	23-10-1996
		FI 962754 A	04-07-1996
		WO 9518794 A	13-07-1995
		HU 76299 A	28-07-1997
		JP 9507241 T	22-07-1997
		ZA 9500057 A	05-01-1996

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/080320 A1

(51) International Patent Classification⁷: C07C 255/54,
A61K 31/277, A61P 5/28, 17/14

(74) Agents: FULLER, Grover, F., Jr. et al.; Pfizer Inc., 201
Tabor Road, Morris Plains, NJ 07950 (US).

(21) International Application Number:
PCT/IB2005/000229

(22) International Filing Date: 31 January 2005 (31.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/544,738 13 February 2004 (13.02.2004) US
60/605,647 30 August 2004 (30.08.2004) US

(71) Applicant (for all designated States except US):
WARNER-LAMBERT COMPANY LLC [US/US];
201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HU, Lain-Yen
[US/US]; Pfizer Global Research and Development, Ann
Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI
48105 (US). LEI, Huangshu [CA/US]; 6E Jacqueline
Road, Waltham, MA 02452 (US). DU, Daniel, Yunlong
[US/US]; Pfizer Global Research and Development, Ann
Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI
48105 (US). LEFKER, Bruce, Allen [US/US]; Pfizer
Global Research and Development, Eastern Point Road,
Groton, CT 06340 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(81) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ANDROGEN RECEPTOR MODULATORS

(57) Abstract: The present invention is directed to a new class of 4-oxo-benzonitriles, their use as androgen modulators, and to their
use in the treatment of alopecia.



WO 2005/080320 A1

-1-

ANDROGEN RECEPTOR MODULATORS

FIELD OF THE INVENTION

5 The present invention is directed to a new class of benzonitriles and to their use as androgen receptor modulators. Other aspects of the invention are directed to the topical use of these compounds to alleviate alopecia and oily skin.

BACKGROUND OF THE INVENTION

10 Alopecia, or balding, is a common problem which medical science has yet to cure. The physiological mechanism by which this hair loss occurs is not known. However, it is known that hair growth is altered in individuals afflicted with alopecia.

Hair follicles undergo cycles of activity involving periods of growth, rest, and shedding. The human scalp typically contains from 100,000 to 350,000 hair fibers or shafts, which undergo metamorphosis in three distinct stages:

15 (a) during the growth phase (anagen) the follicle (i.e., the hair root) penetrates deep into the dermis with the cells of the follicle dividing rapidly and differentiating in the process of synthesizing keratin, the predominant component of hair. In non-balding humans, this growth phase lasts from one to five years;

(b) the transitional phase (catagen) is marked by the cessation of mitosis and lasts from two to several weeks, and;

20 (c) the resting phase (telogen) in which the hair is retained within the scalp for up to 12 weeks, until it is displaced by new follicular growth from the scalp below.

25 In humans, this growth cycle is not synchronized. An individual will have thousands of follicles in each of these three phases. However, most of the hair follicles will be in the anagen phase. In healthy young adults, the anagen to telogen ratio can be as high as 9 to 1. In individuals with alopecia, this ratio can be reduced to as low as 2:1.

-2-

Androgenetic alopecia arises from activation of an inherited sensitivity to androgenic hormones. It is the most common type of alopecia. It affects both men (50%) and women (30%), primarily of Caucasian origin. Gradual changes in the diameter and length of the hair shaft are experienced over time and with increasing age. Terminal hair is gradually converted to short, wispy, colorless vellus hair. As a consequence, men in their 20's and women in their 30's and 40's begin to notice their hair becoming finer and shorter. In males, most of the hair loss occurs at the front and vertex of the head. Females experience a thinning over their entire scalp. As discussed above, the anagen to telogen ratio is reduced significantly, resulting in less hair growth.

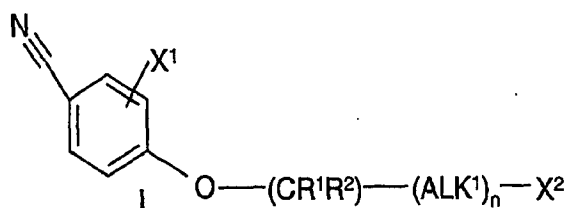
Minoxidil, a potassium channel opener, promotes hair growth. Minoxidil is available commercially in the United States under the trademark ROGAINE®. While the exact mechanism of action of minoxidil is unknown, its impact on the hair growth cycle is well documented. Minoxidil promotes the growth of the hair follicle and increases the period of time that the hair follicle is in the anagen phase (i.e. increases the anagen to telogen ratio).

While minoxidil promotes hair growth, the cosmetic efficacy of this growth can vary widely. For example, Roenigk reported the results of a clinical trial involving 83 males who used a topical solution of 3% minoxidil for a period of 19 months. Hair growth occurred in 55% of the subjects. However, only 20% of the subjects considered the growth to be cosmetically relevant. (Clin.Res., 33, No. 4, 914A, 1985). Tosti reported cosmetically acceptable re-growth in 18.1% of his subjects. (Dermatologica, 173, No. 3, 136-138, 1986). Thus, the need exists in the art for compounds having the ability produce higher rates of cosmetically acceptable hair growth in patients with alopecia.

-3-

SUMMARY OF THE INVENTION

In accordance with the present invention, a new class of 4-oxo-benzonitriles has been discovered. These compounds, and their pharmaceutically acceptable salts, hydrates, and prodrugs thereof, may be represented by the following formula:



in which:

X^1 is represented by halogen or haloalkyl;

X^2 is represented by $-\text{CR}^3\text{R}^4\text{R}^5$, $-\text{CH}=\text{CH}_2$, or $-\text{C}\equiv\text{CH}$;

R^1 , and R^2 , are each independently represented by a substituent selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, haloalkyl, hydroxyalkyl, thiol, and thioalkyl;

R^3 , R^4 , and R^5 are each independently represented by a substituent selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, haloalkyl, hydroxy, hydroxyalkyl, thiol, thioalkyl and $-\text{NR}^6\text{R}^7$;

n is represented by the integer 0 or 1;

ALK^1 is represented by a C_{1-8} linear alkylene group, in which up to 8 hydrogen atoms of the alkylene group may optionally be replaced by a substituent selected from the group consisting of C_{1-6} alkyl, haloalkyl, halogen, hydroxy, hydroxyalkyl, thiol, thioalkyl, and $-\text{NR}^6\text{R}^7$;

R^6 and R^7 are each independently represented by hydrogen or C_{1-6} alkyl with the proviso that:

1) if n is 0 and X^2 is represented by $-\text{CH}=\text{CH}_2$ or $-\text{C}\equiv\text{CH}$, then at least one of R^1 or R^2 is represented by thiol, hydroxyalkyl, or thioalkyl;

-4-

- 2) if n is 1 and X^2 is represented by $-\text{CH}=\text{CH}_2$ or $-\text{C}\equiv\text{CH}$, then in the alternative, at least one of R^1 or R^2 is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl, or at least one hydrogen atom from Alk^1 is replaced by a substituent selected from the group consisting of hydroxy, thiol, hydroxyalkyl, and thioalkyl;
- 3) if n is 0 and X^2 is represented by $-\text{CR}^3\text{R}^4\text{R}^5$, then, in the alternative, at least one of R^1 or R^2 is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl, or at least one of R^3 , R^4 , or R^5 is represented by hydroxy, hydroxyalkyl, thiol, or thioalkyl;
- 4) if n is 1 and X^2 is represented by $-\text{CR}^3\text{R}^4\text{R}^5$, then alternatively: a) at least one of R^1 or R^2 is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl, b) at least one of R^3 , R^4 , or R^5 is represented by a substituent selected from the group consisting of hydroxy, hydroxyalkyl, thiol, and thioalkyl, or c) at least one hydrogen atom of Alk^1 is replaced with a substituent selected from the group consisting of hydroxy, thiol, thioalkyl, and hydroxyalkyl.

The compounds of Formula I are androgen receptor modulators. The compounds have affinity for the androgen receptor and will cause a biological effect by binding to the receptor. Typically, the compounds will act as antagonists. In selected embodiments they will act as partial agonists, full agonists, or tissue selective agonists. As androgen receptor modulators, the compounds can be used to treat, or alleviate, conditions associated with inappropriate activation of the androgen receptor. Examples of such conditions for antagonists include, but are not limited to, acne, excess sebum secretion, androgenic alopecia, hormone dependant cancers such as prostate cancer, and hirsutism. Those compounds which are partial agonists, full agonists, or tissue selective agonists can be used to treat osteoporosis, hypogonadism, anemia, or to stimulate increases in muscle mass, especially in wasting diseases.

The invention is also directed to pharmaceutical compositions containing at least one of the compounds of Formula I, in an amount effective to modulate

-5-

activation of the androgen receptor. In a further embodiment, the invention is directed to an article of manufacture containing a compound of Formula I, packaged for retail distribution, in association with instructions advising the consumer on how to use the compound to alleviate a condition associated with inappropriate activation of the androgen receptor. An additional embodiment is directed to the use of a compound of Formula I as a diagnostic agent to detect inappropriate activation of the androgen receptor.

In a further embodiment, the compounds of Formula I are used topically to induce and/or stimulate hair growth and/or to slow down hair loss. The compounds may also be used topically in the treatment of excess sebum and/or of acne.

DETAILED DESCRIPTION OF THE INVENTION

The headings within this document are only being utilized expedite its review by the reader. They should not be construed as limiting the invention or claims in any manner.

Definitions and Exemplification

As used throughout this application, including the claims, the following terms have the meanings defined below, unless specifically indicated otherwise. The plural and singular should be treated as interchangeable, other than the indication of number:

- a. "halogen" refers to a chlorine, fluorine or bromine atom.
- b. "C₁- C₆ alkyl" refers to a branched or straight chained alkyl group containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pentyl, hexyl, etc.
- c. "haloalkyl" refers to a branched or straight chained alkyl group containing from 1 to 6 carbon atoms, in which at least one hydrogen atom is replaced with a halogen (i.e. C₁-C₆ haloalkyl). Examples of suitable haloalkyl's include chloromethyl, difluoromethyl, trifluoromethyl, 1-fluoro-2-chloro-ethyl, 5-fluoro-hexyl, 3-difluoro-isopropyl, 3-chloro-isobutyl, etc.
- d. "hydroxyalkyl" refers to a branched or straight chained alkyl group containing from 1 to 6 carbon atoms in which at least one

-6-

hydrogen atom is replaced with a hydroxy function (i.e. C₁-C₆ hydroxyalkyl). Examples of suitable hydroxyalkyl's include hydroxymethyl, 1,2-dihydroxy-propyl, 1-hydroxy-pentyl, 6-hydroxy-hexyl, 2-hydroxy-ethyl, etc.

- 5 e. "thioalkyl" refers to a branched or straight chained alkyl group containing from 1 to 6 carbon atoms in which at least one hydrogen atom is replaced with a sulfhydryl group (i.e. -SH). Examples of suitable thioalkyl's include methyl mercaptan, 2-thiol-ethyl, 1,3-dithiol-propyl, 6-thiol-hexyl, 4-thiol-pentyl, etc.
- 10 f. "linear alkylene group containing from 1 to 8 carbon atoms" refers to an alkyl group containing from 1 to 8 carbon atoms serving as a linking group within the molecule (i.e. no terminal -CH₃ function). Examples of such alkyl groups include -CH₂-, -CH₂-(CH₂)₄-CH₂-, -CH₂-(CH₂)₆-CH₂-, -CH₂-CH₂-CH₂-,
- 15 -CH₂-(CH₂)₂-CH₂-, etc.
- g. "solvate" is a crystalline form of a compound or salt thereof, containing one or more molecules of solvent of crystallization, i.e., a compound of Formula I or a salt thereof, containing solvent combined in the molecular form. A "hydrate" is a solvate in which
- 20 the solvent is water.
- h. "polymorph" is a compound or salt thereof, such as the compound of Formula I or a salt thereof, which occurs in at least one crystalline form.
- i. "androgen" refers to testosterone and its precursors and
- 25 metabolites, and 5-alpha reduced androgens, including but not limited to dihydrotestosterone. Androgen refers to androgens from the testis, adrenal gland, and ovaries, as well as all forms of natural, synthetic and substituted or modified androgens.
- j. "pharmaceutically acceptable salts" is intended to refer to
- 30 either pharmaceutically acceptable acid addition salts" or "pharmaceutically acceptable basic addition salts" depending upon actual structure of the compound.
- k. "pharmaceutically acceptable acid addition salts" is
- 35 intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts.

-7-

include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents.

- l. "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by Formula I, or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline.
- m. "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.
- n. "compound of Formula I", "compounds of the invention", and "compounds" are used interchangeably throughout the application and should be treated as synonyms.
- o. "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, stump tail macques, and humans.

-8-

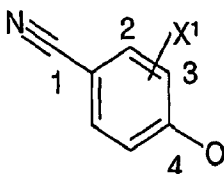
- p. "treat" refers to the ability of the compounds to either relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

5 Some of the compounds of Formula I will exist as optical isomers. Any reference in this application to one of the compounds represented by Formula I is meant to encompass either a specific optical isomer or a mixture of optical isomers (unless it is expressly excluded). The specific optical isomers can be separated and recovered by techniques known in the art such as
10 chromatography on chiral stationary phases or resolution via chiral salt formation and subsequent separation by selective crystallization. Alternatively utilization of a specific optical isomer as the starting material will produce the corresponding isomer as the final product.

15 In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention. A compound can also exist in different polymorphic forms and the
20 claims should be construed as covering all such forms.

 All of the compounds of Formula I contain a phenyl ring. To further exemplify the invention, the numbering system for this ring and its substitution pattern is shown below:

25



-9-

Position 1 of this phenyl ring will always be substituted with a cyano moiety as depicted above. Position 4 will be substituted with an oxygen atom forming an ether moiety. The phenyl ring will be further substituted, as depicted by X¹, at position 2 or 3 with a halogen atom or a haloalkyl moiety. Typically, this
5 halogen or haloalkyl moiety will be at the 2-position. More typically it will be trifluoroalkyl, located at the 2-position of the phenyl ring.

As noted above, position 4 of the phenyl ring is substituted with an ether moiety, which will always include: $-(CR^1R^2)-(ALK^1)_n-X^2$. Alk¹, when present,
10 represents a C₁ to C₈ linear alkylene moiety, such as methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, or octylene. Up to 8 hydrogen atoms of this alkylene moiety may be replaced with one of the substituents defined above. Any single carbon atom of Alk¹ may be unsubstituted, monosubstituted, or disubstituted. These carbon atoms may be
15 substituted with the same substituent or differing substituents.

The ether moiety $-(CR^1R^2)-(ALK^1)_n-X^2$ will be substituted with at least one hydroxy, thiol, hydroxyalkyl, or thioalkyl moiety. This may be accomplished by one of two alternative substitution patterns (depending upon the presence, or
20 absence of Alk¹). If Alk¹ is not present in the molecule (i.e. n is 0), then one of, R³, R⁴, or R⁵ may be represented by hydroxy, hydroxyalkyl, thiol, or thioalkyl, or one of R¹ or R² may be represented by hydroxyalkyl, thiol, or thioalkyl. If Alk¹ is present (i.e. n is 1), then alternatively: a) one of R³, R⁴, or R⁵ may be represented by hydroxy, hydroxyalkyl, thiol, or thioalkyl, b) one of R¹ or R² may be
25 represented by hydroxyalkyl, thiol, or thioalkyl, or c) , one of the carbon atoms of Alk¹ may be substituted with hydroxy, hydroxyalkyl, thiol, or thioalkyl.

This requirement that the molecule contain a hydroxy or thiol function should not be construed as limiting the molecule to only one hydroxy or thiol
30 moiety. If desired, the ether moiety $-(CR^1R^2)-(ALK^1)_n-X^2$ may contain multiple hydroxy, hydroxyalkyl, thioalkyl and thiol functions consistent with the substitution pattern described above.

In a further optional embodiment of the invention, for those compounds in
35 which X² is CR³R⁴R⁵ and n is 0; at least one of R¹, R², R³, R⁴, or R⁵ is represented by C₁-C₈ alkyl, haloalkyl, thioalkyl, or hydroxyalkyl (i.e. the ether

-10-

residue, $-\text{CR}^1\text{R}^2-(\text{Alk}^1)_n-\text{X}^2$, is branched alkyl). In an additional optional embodiment, for those compound in which X^2 is $\text{CR}^3\text{R}^4\text{R}^5$ and n is 1; at least one of R^1 , R^2 , R^3 , R^4 , or R^5 is represented by C_1 - C_6 alkyl, haloalkyl, thioalkyl, or hydroxyalkyl or alternatively one hydrogen atom of Alk^1 is replaced with a substituent selected from the group consisting of C_1 - C_6 alkyl, haloalkyl, thioalkyl, or hydroxyalkyl (i.e. the ether residue, $-\text{CR}^1\text{R}^2-(\text{Alk}^1)_n-\text{X}^2$, is branched alkyl).

More specific embodiments of the invention are directed to compounds of Formula I in which:

- 1) X^1 is CF_3 and is located at the 2-position of the phenyl ring and X^2 is $\text{CR}^3\text{R}^4\text{R}^5$, in which one of R^3 , R^4 , or R^5 is hydroxy;
- 2) X^1 is Cl and is located at the 2-position of the phenyl ring and X^2 is $\text{CR}^3\text{R}^4\text{R}^5$, in which one of R^3 , R^4 , or R^5 is hydroxy;
- 3) X^1 is CF_3 and is located at the 2-position of the phenyl ring, R^1 is hydrogen and R^2 is C_1 - C_6 alkyl, n is 1 in which Alk^1 is methylene, ethylene, propylene, or butylenes, X^2 is $-\text{CR}^3\text{R}^4\text{R}^5$, in which R^3 is hydrogen or C_1 - C_6 alkyl, R^4 is hydrogen or C_1 - C_6 alkyl, and R^5 is hydroxy;
- 4) X^1 is CF_3 and is located at the 2-position of the phenyl ring, R^1 is hydrogen or C_1 - C_6 alkyl, R^2 is hydrogen, n is 0, and X^2 is $\text{CR}^3\text{R}^4\text{R}^5$, in which R^3 is hydroxy or hydroxylalkyl, R^4 is hydrogen or C_1 - C_6 alkyl and R^5 is hydrogen; or
- 5) X^1 is CF_3 or Cl , and is located at the 2-position of the phenyl ring, R^1 and R^2 are each hydrogen, n is 1 in which Alk^1 is methylene, ethylene, propylene, or butylene, which is substituted with 1 to 3 substituents independently selected from hydroxy, hydroxyalkyl or C_1 - C_6 alkyl and X^2 is $\text{CR}^3\text{R}^4\text{R}^5$, in which R^3 is hydrogen or hydroxy, and R^4 and R^5 are each hydrogen or C_1 - C_6 alkyl.

More specific examples of compounds encompassed by Formula I include:

- i) 4-(2-hydroxy-1-ethyl-propoxy)-2-trifluoromethyl-benzonitrile;
- ii) 4-(2-hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile;

-11-

- iii) 4-(3-hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
- iv) 4-(2-hydroxy-6-methyl-heptyloxy)-2-trifluoromethyl-benzonitrile;
- 5 v) 4-(2-hydroxy-7-hydroxy-heptyloxy)-2-trifluoromethyl-benzonitrile;
- vi) 4-(2-hydroxy-octyloxy)-2-trifluoromethyl-benzonitrile;
- vii) 4-(2-hydroxy-8-hydroxy-8methyl-octyloxy)-2-trifluoromethyl-benzonitrile;
- 10 viii) 4-(2-hydroxy-oct-7-enyloxy)-2-trifluoromethyl-benzonitrile;
- ix) 4-(2-hydroxy-oct-7-ynyloxy)-2-trifluoromethyl-benzonitrile;
- x) 4-(2-ethyl-3-Hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
- xi) 4-(3-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
- xii) 4-(3-hydroxy-hex-5-enyloxy)-2-trifluoromethyl-benzonitrile;
- 15 xiii) 4-(3-hydroxy-hex-5-ynyloxy)-2-trifluoromethyl-benzonitrile;
- xiv) 4-(3-hydroxy-2-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
- xv) 4-(3-hydroxy-2-propyl-butoxy)-2-trifluoromethyl-benzonitrile;
- 20 xvi) 4-(3-hydroxy-2, 2-dimethyl-propoxy)-2-trifluoromethyl-benzonitrile;
- xvii) 4-(3-hydroxy-3-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
- xviii) 4-(4-hydroxy-3-methyl-pentoxy)-2-trifluoromethyl-benzonitrile;
- 25 xix) 4-(3-hydroxy-2,2,4-trimethyl-pentyloxy)-2-trifluoromethyl-benzonitrile;
- xx) 4-(2-ethyl-3-Hydroxy-hexyloxy)-2-trifluoromethyl-benzonitrile;
- 30 xxi) 4-[2-(1-hydroxy-ethyl)-hexyloxy]-2-trifluoromethyl-benzonitrile;
- xxii) 4-(3-hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
- xxiii) 4-(3-hydroxy-1-methyl-2-ethyl-butoxy)-2-trifluoromethyl-benzonitrile
- 35 xxiv) 4-(4-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;

-12-

- xxv) 4-(6-hydroxy-heptoxy)-2-trifluoromethyl-benzonitrile;
xxvi) 4-(4-Hydroxy-heptyloxy)-2-trifluoromethyl-benzonitrile;
xxvii) 4-(4-hydroxy-1-propyl-butoxy)-2-trifluoromethyl-
benzonitrile;
5 xxviii) 4-(4-hydroxy-1-methyl-pentyloxy)-2-trifluoromethyl-
benzonitrile;
xxix) 4-(5-hydroxy-pentyloxy)-2-trifluoromethyl-benzonitrile;
xxx) 4-(5-hydroxy-hexyloxy)-2-trifluoromethyl-benzonitrile;
xxxi) 4-(5-hydroxy-3-methyl-pentyloxy)-2-trifluoromethyl-
10 benzonitrile;
xxxii) 2-chloro-4-(3-hydroxy-2,2,4-trimethyl-pentyloxy)-
benzonitrile;
xxxiii) 2-chloro-4-(4-hydroxy-butoxy)-benzonitrile;
xxxiv) 2-chloro-4-(3-hydroxy-propoxy)-benzonitrile;
15 xxxv) 2-chloro-4-(1-hydroxymethyl-allyloxy)-benzonitrile;
xxxvi) 2-chloro-4-(1-hydroxymethyl-acetyleneloxy)-benzonitrile;
xxxvii) 2-chloro-4-(3-hydroxy-2-methyl-propoxy)-benzonitrile;
xxxviii) 2-chloro-4-(5-hydroxy-pentyloxy)-benzonitrile;
xxxix) 2-chloro-4-(4-hydroxy-1-methyl-pentyloxy)-benzonitrile, or;
20 xl) 2-chloro-4-(5-hydroxy-3-methyl-pentyloxy)-benzonitrile.

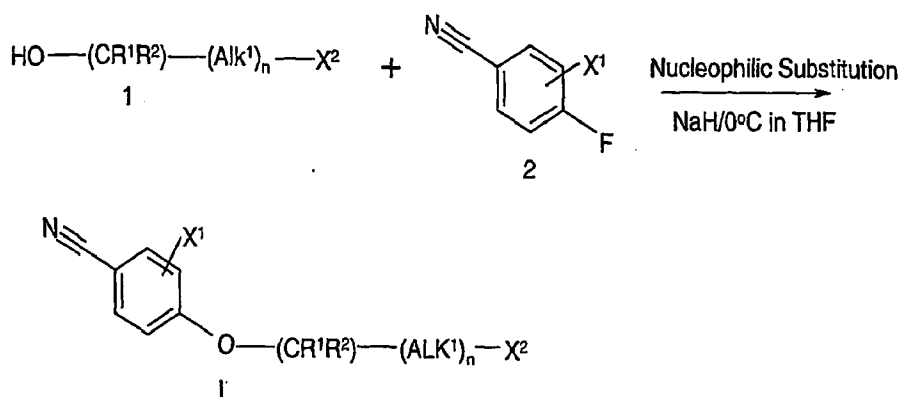
Synthesis

- 25 The compounds of Formula I can be prepared using methods analogous to those known in the art for the preparation of ethers. The reader's attention is directed to European Patent Application Number 58932, published September 1, 1982, the contents of which are hereby incorporated by reference for a description of such reactions. Scheme I below provides an overview of one such technique:

30

-13-

SCHEME I



5

As depicted above, one of the starting materials is an alcohol as depicted by structure 1. R^1 , R^2 , Alk^1 and X^2 should be represented by the same substituent as is desired in the final product. These alcohols are known in the art and may be purchased from known commercial sources. Alternatively, they can be prepared as described in Tetrahedron: Asymmetry, 1991 Vol. 2, page 569.

10

The other starting material is a 4-fluoro-benzonitrile as depicted by structure 2. X^1 should be represented by the same substituent as desired in the final product. These benzonitriles are known in the art and may be synthesized as described by Japanese Patent Application Number 01097937.

15

The nucleophilic substitution depicted above may be carried out as is known in the art. The alcohol of structure 1 is contacted with a slight excess of a base, such as sodium hydride, to produce an alkoxide ion. The reaction is carried out in an aprotic solvent, such as tetrahydrofuran, under an inert atmosphere (typically nitrogen) at a temperature of about 0°C . The alcohol is stirred with the base for a period of time ranging from 5 to 60 minutes.

20

One equivalent of the 4-fluoro-benzonitrile of structure 2 is then added to the reaction medium and the reactants are stirred for a sufficient period of time to allow the alkoxide ion to displace the fluorine from the benzonitrile. This typically takes from 30 minutes to 24 hours. The reaction is typically allowed to warm to room temperature.

25

-14-

The desired product of Formula I can be recovered by extraction, evaporation, or other techniques known in the art. It may then be optionally purified by chromatography, recrystallization, distillation, or other techniques known in the art.

As would be appreciated by those skilled in the art, some of the methods useful for the preparation of such compounds, as discussed above, may require protection of a particular functionality, e.g., to prevent interference by such functionality in reactions at other sites within the molecule or to preserve the integrity of such functionality. The need for, and type of, such protection is readily determined by one skilled in the art, and will vary depending on, for example, the nature of the functionality and the conditions of the selected preparation method. See, e.g., T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Some of the compounds of this invention are acidic and they form salts with a pharmaceutically acceptable cation. Some of the compounds of this invention are basic and form salts with pharmaceutically acceptable anions. All such salts are within the scope of this invention and they can be prepared by conventional methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compounds are obtained in crystalline form according to procedures known in the art, such as by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

Medical and Cosmetic Uses

The compounds of Formula I are androgen receptor modulators. They can be used to alleviate conditions associated with inappropriate activation of the androgen receptor. Compounds acting as androgen antagonists may be used to

-15-

treat, or alleviate, hormone dependent cancers such as prostate carcinomas, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, hypertrichosis, precocious puberty, prostamegaly, virilization, and polycystic ovary syndrome. Compounds acting as partial agonists, or full agonists, may be used to treat, or alleviate, male hypogonadism, male sexual dysfunction (impotence, male dysspermtatogenic sterility), abnormal sex differentiation (male hermaphroditism), male delayed puberty, male infertility, aplastic anemia, hemolytic anemia, sickle cell anemia, idiopathic thrombocytopenic purpura, myelofibrosis, renal anemia, wasting diseases (post operative, malignant tumor, trauma, chronic renal disease, burn or AIDS induced), abatement of pain in terminal carcinoma of female genitalia, inoperable breast cancer, mastopathy, endometriosis, female sexual dysfunction, osteoporosis, wound healing and muscle tissue repair.

In order to exhibit the therapeutic properties described above, the compounds need to be administered in a quantity sufficient to modulate activation of the androgen receptor. This amount can vary depending upon the particular disease/condition being treated, the severity of the patient's disease/condition, the patient, the particular compound being administered, the route of administration, and the presence of other underlying disease states within the patient, etc. When administered systemically, the compounds typically exhibit their effect at a dosage range of from about 0.1 mg/kg/day to about 100 mg/kg/day for any of the diseases or conditions listed above. Repetitive daily administration may be desirable and will vary according to the conditions outlined above.

The compounds of the present invention may be administered by a variety of routes. They are effective if administered orally. The compounds may also be administered parenterally (i.e. subcutaneously, intravenously, intramuscularly, intraperitoneally, or intrathecally), rectally, or topically.

In a typical embodiment, the compounds are administered topically. Topical administration is especially appropriate for hirsutism, alopecia, acne and excess sebum. The dose will vary, but as a general guideline, the compound will be present in a dermatologically acceptable carrier in an amount of from about 0.01 to 50 w/w%, and more typically from about 0.1 to 10 w/w%. The

-16-

dermatological preparation will be applied to the affected area from 1 to 4 times daily. "Dermatologically acceptable" refers to a carrier which may be applied to the skin or hair, and which will allow the drug to diffuse to the site of action. More specifically, it refers the site where inhibition of activation of an androgen receptor is desired.

In a further embodiment, the compounds are used topically to relieve alopecia, especially androgenic alopecia. Androgens have a profound effect on both hair growth and hair loss. In most body sites, such as the beard and pubic skin, androgens stimulate hair growth by prolonging the growth phase of the hair cycle (anagen) and increasing follicle size. Hair growth on the scalp does not require androgens but, paradoxically, androgens are necessary for balding on the scalp in genetically predisposed individuals (androgenic alopecia) where there is a progressive decline in the duration of anagen and in hair follicle size. Androgenic alopecia is also common in women where it usually present as a diffuse hair loss rather than showing the patterning seen in men.

While the compounds will most typically be used to alleviate androgenic alopecia, the invention is not limited to this specific condition. The compounds may be used to alleviate any type of alopecia. Examples of non-androgenic alopecia include alopecia areata, alopecia due to radiotherapy or chemotherapy, scarring alopecia, stress related alopecia, etc. As used in this application, "alopecia" refers to partial or complete hair loss on the scalp.

Thus, the compounds can be applied topically to the scalp and hair to prevent, or alleviate balding. Further, the compound can be applied topically in order to induce or promote the growth of hair on the scalp.

In a further embodiment of the invention, a compound of Formula I is applied topically in order to prevent the growth of hair in areas where such hair growth is not desired. One such use will be to alleviate hirsutism. Hirsutism is excessive hair growth in areas that typically do not have hair (i.e. a female face). Such inappropriate hair growth occurs most commonly in women and is frequently seen at menopause. The topical administration of the compounds will alleviate this condition leading to a reduction, or elimination of this inappropriate, or undesired, hair growth.

-17-

The compounds may also be used topically to decrease sebum production and more specifically to alleviate oily skin. Likewise the compounds can be used topically to alleviate acne.

5 In a further embodiment, those compounds acting as partial agonists, or full agonists, may be used to treat, or alleviate, osteoporosis. Osteoporosis is characterized by bone loss, resulting from an imbalance between bone resorption (destruction) and bone formation, which starts in the fourth decade and continues throughout life at the rate of about 1-4% per year (Eastell, Treatment of
10 postmenopausal osteoporosis, New Eng. J. Med. 338: 736, 1998). In the United States, there are currently about 20 million people with detectable fractures of the vertebrae due to osteoporosis. In addition, there are about 250,000 hip fractures per year due to osteoporosis, associated with a 12%-20% mortality rate within the first two years, while 30% of patients require nursing home care after the fracture
15 and many never become fully ambulatory again. In postmenopausal women, estrogen deficiency leads to increased bone resorption resulting in bone loss in the vertebrae of around 5% per year, immediately following menopause. Thus, first line treatment/prevention of this condition is inhibition of bone resorption by bisphosphonates, estrogens, selective estrogen receptor modulators (SERMs)
20 and calcitonin. However, inhibitors of bone resorption are not sufficient to restore bone mass for patients who have already lost a significant amount of bone. The increase in spinal BMD attained by bisphosphonate treatment can reach 11% after 7 years of treatment with alendronate. In addition, as the rate of bone turnover differs from site to site; higher in the trabecular bone of the vertebrae
25 than in the cortex of the long bones, the bone resorption inhibitors are less effective in increasing hip BMD and preventing hip fracture. Therefore, osteoanabolic agents, which increase cortical/periosteal bone formation and bone mass of long bones, would address an unmet need in the treatment of osteoporosis especially for patients with high risk of hip fractures.

30 A number of studies demonstrate that androgens are osteoanabolic in women and men. Anabolic steroids, such as nandrolone decanoate or stanozolol, have been shown to increase bone mass in postmenopausal women. Beneficial effects of androgens on bone in post- menopausal osteoporosis are well documented in recent studies using combined testosterone and estrogen

-18-

administration (Hofbauer, et al., Androgen effects on bone metabolism: recent progress and controversies, Eur. J. Endocrinol. 140, 271-286, 1999). Thus those compounds of Formula I exhibiting agonist or partial agonist activity may be used to treat, or alleviate, osteoporosis, including primary osteoporosis such as senile, postmenopausal and juvenile osteoporosis, as well as secondary osteoporosis, such as osteoporosis due to hyperthyroidism or Cushing syndrome (due to corticosteroid treatment), acromegaly, hypogonadism, dysosteogenesis and hypophosphatasemia. Other bone related indications amenable to treat from androgen agonists include osteoporotic fracture, childhood idiopathic bone loss, alveolar bone loss, mandibular bone loss, bone fracture, osteotomy, periodontitis, or prosthetic ingrowth.

Those compounds acting as agonists, or partial agonists, can also be used to stimulate muscle mass in patients afflicted with wasting diseases, such as AIDS, cancer cachexia, burns, renal disease, etc. Patients suffering from trauma, bedsores, age, etc. can also benefit from the anabolic effects of androgens.

Co-Administration

In a further embodiment of the invention, the compounds of Formula I can be co-administered with other compounds to further enhance their activity, or to minimize potential side effects. For example, potassium channel openers, such as minoxidil, are known to stimulate hair growth and to induce anagen. Examples of other potassium channel openers include (3S,4R)-3,4-dihydro-4-(2,3-dihydro-2-methyl-3-oxopyridazin-6-yl)oxy-3-hydroxy-6-(3-hydroxyphenyl)sulphonyl-2,2,3-trimethyl-2H-benzo[b]pyran, diaxozide, and PO 1075 which is under development by Leo Pharmaceuticals. Thyroid hormone is also known to stimulate hair growth. Synthetic thyroid hormone replacements (i.e. thyromimetics) have also been shown to stimulate hair growth. Such thyromimetics have been described in the literature previously. The reader's attention is directed to European Patent Application No. 1262177, the contents of which are hereby incorporated by reference, for a discussion of such

-19-

compounds and their use to alleviate alopecia. One particular compound of interest is 2-{4-[3-(4-Fluoro-benzyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-2H-[1,2,4]triazine-3,5-dione. Anti-androgens can work by a number of different mechanisms. For example, some compounds block the conversion of testosterone to 5- α -dihydrotestosterone, which is responsible for the biological effect in many tissues. 5-Alpha-reductase inhibitors, such as finasteride, have been shown to stimulate hair growth. Finasteride is commercially available from Merck under the trade name Propecia®. Examples of other 5- α -reductase inhibitors include dutasteride (Glaxo Smithkline). Such compounds can be co-administered with the compounds of Formula I to alleviate alopecia.

Protein kinase C inhibitors have also been shown to stimulate hair growth and induce anagen. Calphostin C, which is a selective inhibitor of protein kinase C, has been shown to induce anagen. Other selective protein kinase C inhibitors, such as hexadecylphosphocholine, palmitoyl-DL-carnitine chloride, and polymyxin B sulfate have also been shown to induce anagen. Skin Pharmacol Appl Skin Physiol 2000 May-Aug;13(3-4):133-42 Any such protein kinase C inhibitor can be co-administered with a compound of Formula I to alleviate alopecia.

Immunophilins are a family of cytoplasmic proteins. Their ligands include cyclosporin, FK506, and rapamycin. They are derived from fungi and were developed primarily for their potent immunosuppressive properties. Cyclosporin binds to the protein, cyclophilin, while FK506 and rapamycin bind to FK binding protein (FKBP). All of these compounds have been shown to stimulate hair growth and induce anagen. Any such immunophilin ligands can be co-administered with a compound of Formula I to alleviate alopecia.

As used in this application, co-administered refers to administering a compound of Formula I with a second anti-alopecia agent, typically having a differing mechanism of action, using a dosing regimen that promotes hair growth in the patient. This can refer to simultaneous dosing, dosing at different times during a single day, or even dosing on different days. The compounds can be

-20-

administered separately or can be combined into a single formulation.

Techniques for preparing such formulations are described below.

Formulations

5 If desired, the compounds can be administered directly without any carrier. However, to ease administration, they will typically be formulated into pharmaceutical carriers. Likewise, they will most typically be formulated into dermatological, or cosmetic carriers. In this application the terms "dermatological carrier" and "cosmetic" carrier are being used interchangeably. They refer to
10 formulations designed for administration directly to the skin or hair.

 Pharmaceutical and cosmetic compositions can be manufactured utilizing techniques known in the art. Typically an effective amount of the compound will be admixed with a pharmaceutically/cosmetically acceptable carrier.

15 For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions, or emulsions. Solid unit dosage forms can be capsules of the ordinary gelatin type containing, for example, surfactants, lubricants and inert
20 fillers such as lactose, sucrose, and cornstarch or they can be sustained release preparations.

 In another embodiment, the compounds of Formula I can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in
25 combination with binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent, which may also contain suspending agents, sweetening agents, flavoring agents,
30 and preservative agents as are known in the art.

 For parenteral administration the compounds may be dissolved in a physiologically acceptable pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers are water,

-21-

saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, buffers, etc., as are known in the art. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid as is known in the art.

The compounds of this invention will typically be administered topically. As used herein, topical refers to application of the compounds (and optional carrier) directly to the skin and/or hair. The topical composition according to the present invention can be in the form of solutions, lotions, salves, creams, ointments, liposomes, sprays, gels, foams, roller sticks, or any other formulation routinely used in dermatology.

Thus, a further embodiment relates to cosmetic or pharmaceutical compositions, in particular dermatological compositions, which comprise at least one of the compounds corresponding to Formula I above. Such dermatological compositions will contain from 0.001% to 10% w/w% of the compounds in admixture with a dermatologically acceptable carrier, and more typically, from 0.1 to 5 w/w% of the compounds. Such compositions will typically be applied from 1 to 4 times daily. The reader's attention is directed to Remington's Pharmaceutical Science, Edition 17, Mack Publishing Co., Easton, PA for a discussion of how to prepare such formulations.

The compositions according to the invention can also consist of solid preparations constituting cleansing soaps or bars. These compositions are prepared according to the usual methods.

The compounds can also be used for the hair in the form of aqueous, alcoholic or aqueous-alcoholic solutions, or in the form of creams, gels, emulsions or mousses, or alternatively in the form of aerosol compositions also comprising a propellant under pressure. The composition according to the invention can also be a hair care composition, and in particular a shampoo, a hair-setting lotion, a treating lotion, a styling cream or gel, a dye composition, a lotion or gel for preventing hair loss, etc. The amounts of the various constituents in the dermatological compositions according to the invention are those conventionally used in the fields considered.

-22-

The medicinal and cosmetics containing the compounds of the invention will typically be packaged for retail distribution (i.e. an article of manufacture). Such articles will be labeled and packaged in a manner to instruct the patient how to use the product. Such instructions will include the condition to be treated, duration of treatment, dosing schedule, etc.

The compounds of Formula I may also be admixed with any inert carrier and utilized in laboratory assays in order to determine the concentration of the compounds within the serum, urine, etc., of the patient as is known in the art. The compounds may also be used as a research tool.

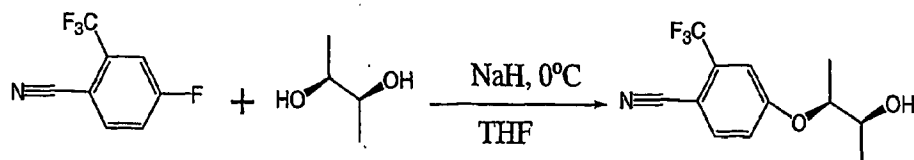
While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention. The following examples and biological data is being presented in order to further illustrate the invention. This disclosure should not be construed as limiting the invention in any manner.

-23-

EXAMPLE 1

(1S,2S)-4-(2-Hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile

5



NaH (0.20g, 4.14 mmol) was suspended in 15 ml of dry THF, then (2S,3S)-(+)-2,3-butanediol was added (0.32g, 3.45 mmol, in 5 ml of dry THF). This mixture was stirred at 0°C for 10 minutes, followed by the addition of 4-fluoro-2-trifluoromethyl-benzonitrile. The reaction mixture was stirred, 0°C for 1 hour, under a nitrogen atmosphere. The mixture was then stirred for an additional 2 hours, at room temperature, in a hood. The reaction was quenched with 25 ml of distilled water, extracted with ethyl acetate (3 x 20 ml). The product was purified by column chromatography, using hexane: ethyl acetate=5:1 to 1:1 as elute to yield the pure product.

MS: 260.0 (M+1 for C₁₂H₁₂F₃NO₂). LCMS: C-18 Column (50%H₂O / 50%CH₃CN), Ret. Time: 1.81 min

20

EXAMPLES 2-27

Using the general procedure of Example 1, but substituting the relevant starting materials, the compounds described in Table I were prepared. Chromatography was performed on a Foxy 200 fraction collector, using prepared Biotage Silicon Gel column, (water:methylnitrile was used as the elute solvent, 50:50, in all examples except 8,16, 17, 26 which utilized a 25:75 admixture of water:methylnitrile). The mass spectra in Table I were recorded with an Hewlett Packard mass spectrometer.

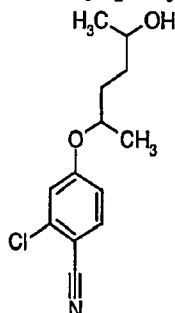
30

TABLE 1				
Example	Structure	Name	RT	Base Peak
2		(1R,2R)-4-(2-Hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile	1.85	MS: 260.0 (M+1 for C ₁₂ H ₁₂ F ₃ NO ₂)
3		4-(2-Hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile	1.80	MS: 260.0 (M+1 for C ₁₂ H ₁₂ F ₃ NO ₂)
4		4-(2-Hydroxy-6-methyl-heptyloxy)-2-trifluoromethyl-benzonitrile	1.95	MS: 316.2 (M+1 for C ₁₆ H ₂₀ F ₃ NO ₂)
5		4-(2-Hydroxy-octyloxy)-2-trifluoromethyl-benzonitrile	1.76	MS: 316.2 (M+1 for C ₁₆ H ₂₀ F ₃ NO ₂)
7		4-(3-Hydroxy-butoxy)-2-trifluoromethyl-benzonitrile	2.50	MS: 260.1 (M+1 for C ₁₂ H ₁₂ F ₃ NO ₂)

8		(3S)-4-(3-Hydroxy-butoxy)-2-trifluoromethyl-benzonitrile	0.91	MS: 260.1 (M+1 for C ₁₂ H ₁₂ F ₃ NO ₂)
9		4-(3-Hydroxy-hex-5-enyloxy)-2-trifluoromethyl-benzonitrile	2.42	MS: 280.0 (M+1 for C ₁₄ H ₁₄ F ₃ NO ₂)
10		4-(3-Hydroxy-2-methyl-butoxy)-2-trifluoromethyl-benzonitrile	2.12	MS: 274.0 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂)
11		4-(3-Hydroxy-2,2-dimethyl-propoxy)-2-trifluoromethyl-benzonitrile		
12		4-(3-Hydroxy-3-methyl-butoxy)-2-trifluoromethyl-benzonitrile	2.25	MS: 274.1 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂)
13		4-(3-Hydroxy-2,2,4-trimethyl-pentyloxy)-2-trifluoromethyl-benzonitrile		
14		4-(2-Ethyl-3-Hydroxy-hexyloxy)-2-trifluoromethyl-benzonitrile	3.8	MS: 316,2 (M+1 for C ₁₆ H ₂₀ F ₃ NO ₂)
15		4-[2-(1-Hydroxy-ethyl)-hexyloxy]-2-trifluoromethyl-benzonitrile	1.6	MS: 316,2 (M+1 for C ₁₆ H ₂₀ F ₃ NO ₂)
16		(1S,3S)-4-(3-Hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile	1.03	MS: 274.0 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂)
17		(1R,3R)-4-(3-Hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile	1.02	MS: 274.0 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂)

18		4-(4-Hydroxybutoxy)-2-trifluoromethylbenzonitrile		MS: 260.0 (M+1 for C ₁₂ H ₁₂ F ₃ NO ₂).
19		4-(4-Hydroxy-2-methylbutoxy)-2-trifluoromethylbenzonitrile	1.52	MS: 274.0 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂).
20		4-(4-Hydroxy-1-heptyloxy)-2-trifluoromethylbenzonitrile	3.10	MS: 302.1 (M+1 for C ₁₅ H ₁₈ F ₃ NO ₂).
21		4-(4-Hydroxy-1-propyl-butoxy)-2-trifluoromethylbenzonitrile	3.16	MS: 302.1 (M+1 for C ₁₅ H ₁₈ F ₃ NO ₂).
22		4-(4-Hydroxy-1-methyl-pentyloxy)-2-trifluoromethylbenzonitrile	2.27	MS: 288.1 (M+1 for C ₁₄ H ₁₆ F ₃ NO ₂).
23		(1S,4S)-4-(4-Hydroxy-1-methyl-pentyloxy)-2-trifluoromethylbenzonitrile	2.29	MS: 288.1 (M+1 for C ₁₄ H ₁₆ F ₃ NO ₂).
24		4-(5-Hydroxypentyloxy)-2-trifluoromethylbenzonitrile	1.94	MS: 274.0 (M+1 for C ₁₃ H ₁₄ F ₃ NO ₂).
25		4-(5-Hydroxyhexyloxy)-2-trifluoromethylbenzonitrile	2.31	MS: 288.0 (M+1 for C ₁₄ H ₁₆ F ₃ NO ₂).
26		4-(5-Hydroxy-3-methyl-pentyloxy)-2-trifluoromethylbenzonitrile	1.01	MS: 288.2 (M+1 for C ₁₄ H ₁₆ F ₃ NO ₂).
27		2-Chloro-4-(3-Hydroxy-2,2,4-trimethyl-pentyloxy)-benzonitrile	1.70	MS: 282.1 (M+1 for C ₁₅ H ₂₀ ClNO ₂).
6		4-(2-Hydroxy-oct-7-enyloxy)-2-trifluoromethylbenzonitrile	3.19	MS: 314.1 (M+1 for C ₁₆ H ₁₈ F ₃ NO ₂).

-27-

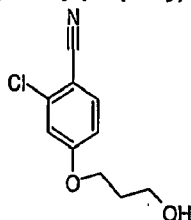
EXAMPLE 28**2-Chloro-4-(4-hydroxy-1-methyl-pentyloxy)-benzonitrile**

5

10

To a solution of 2,5-hexanediol (28 mg, 0.240 mmol) in tetrahydrofuran was added an excess of potassium butoxide. The admixture was stirred, briefly, and 2-chloro-4-fluoro-benzonitrile (37 mg, 0.240 mmol) was added. The admixture was stirred at room temperature for 72 hours. Purification by reverse phase high pressure chromatography eluting with a solvent gradient (15% of 0.1% formic acid / CH₃CN in 0.1% formic acid / water to 100% of 0.1% formic acid / water) provided 28.4 mg of 2-chloro-4-(4-hydroxy-1-methyl-pentyloxy)-benzonitrile. ¹H NMR (CDCl₃) δ 7.50 (d, 1H), 6.95 (m, 1H), 6.79 (br d, 1H), 4.43 (m, 1H), 3.79 (m, 1H), 1.89-1.40 (m, 4H), 1.30 (d, 3H), 1.17 (d, 3H); MS m/z 253.

15

EXAMPLE 29**2-Chloro-4-(3-hydroxy-propoxy)-benzonitrile**

20

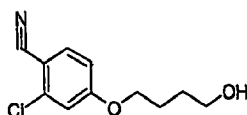
25

To 1,3-propanediol (320 mg, 4.2 mmol) was added sodium (21 mg, 0.92 mmol). The mixture is stirred at room temperature for 10 minutes and 2-chloro-4-fluoro-benzonitrile (156 mg, 1.0 mmol) was added. The reaction was heated to 105°C for 24 hours. The reaction was cooled to room temperature, was diluted with water and was extracted with Et₂O (3x). The organic solution was dried (MgSO₄), filtered and concentrated. The residue was purified by reverse phase high pressure chromatography eluting with a solvent gradient (15% of 0.1% formic acid / CH₃CN in 0.1% formic acid / water to 100% of 0.1% formic acid /

-28-

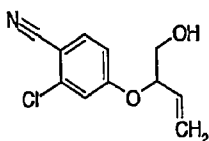
water) to provide 107 mg of 2-chloro-4-(3-hydroxy-propoxy)-benzonitrile. ^1H NMR (CDCl_3) δ 7.54 (d, 1H), 7.00 (m, 1H), 6.85 (dd, 1H), 4.15 (t, 2H), 3.83 (t, 2H), 2.04 (m, 2H).

5

EXAMPLE 30**2-Chloro-4-(4-hydroxy-butoxy)-benzonitrile**

Following the procedure described for Example 29, 1,4-butanediol (1 mL, 10 mmol) was reacted with 2-chloro-4-fluoro-benzonitrile (159 mg, 1.0 mmol) for 24 hours at room temperature. Purification by reverse phase high pressure chromatography eluting with a solvent gradient (15% of 0.1% formic acid / CH_3CN in 0.1% formic acid / water to 100% of 0.1% formic acid / water) provided 10 mg of 2-chloro-4-(4-hydroxy-butoxy)-benzonitrile. ^1H NMR (CDCl_3) δ 7.54 (d, 1H), 6.98 (d, 1H), 6.83 (dd, 1H), 4.03 (t, 2H), 3.71 (t, 2H), 1.90 (m, 2H), 1.72 (m, 2H); MS 226.1 (M+1).

15

EXAMPLE 31**2-Chloro-4-(1-hydroxymethyl-allyloxy)-benzonitrile**

20

Step A: 1-(tert-Butyl-dimethyl-silanyloxy)-but-3-en-2-ol

To a solution of (+/-)-3-butene-1,2-diol (500 mg, 5.67 mmol) in CH_2Cl_2 (25 mL) was added imidazole (444 mg, 6.53 mmol). The solution was cooled to 0°C and t-butyldimethylsilyl chloride (1.0 M in THF, 6.24 mL, 6.24 mmol) was added. The reaction was stirred at 0°C for 15 minutes and at room temperature for 1 hour and 30 minutes. The mixture was diluted with aqueous NH_4Cl and extracted with CH_2Cl_2 (3x). The organic solution was washed with brine, dried (MgSO_4), filtered and concentrated. The residue was purified by medium pressure chromatography eluting with a solvent gradient (5% EtOAc in hexanes to 100% EtOAc) to provide 827.5 mg of 1-(tert-butyl-dimethyl-silanyloxy)-but-3-en-2-ol. ^1H NMR (CDCl_3) δ

25

30

-29-

5.81 (m, 1H), 5.34 (d, 1H), 5.19 (d, 1H), 4.17 (m, 1H), 3.66 (dd, 1H), 3.45 (dd, 1H), 0.90 (s, 9H), 0.08 (s, 6H); MS m/z 202.

Step B: 4-[1-(tert-Butyl-dimethyl-silyloxy)-allyloxy]-2-chloro-benzonitrile

5

10

15

To a solution of 1-(tert-butyl-dimethyl-silyloxy)-but-3-en-2-ol (1.102 g, 5.45 mmol) in THF (26 mL) at -78°C was added potassium tert-butoxide (1.0M in THF, 5.99 mL, 5.99 mmol). The solution was stirred for 15 minutes and 2-chloro-4-fluoro-benzonitrile (847 mg, 5.45 mmol) was added at -78°C . The reaction was stirred at room temperature for 24 hours, quenched with water and extracted with EtOAc (3x). The organic solution was washed with water and brine, dried (MgSO_4), filtered and concentrated to provide 1.67 g of a 1:1 mixture of 4-[1-(tert-butyl-dimethyl-silyloxy)-allyloxy]-2-chloro-benzonitrile and 4-[2-(tert-butyl-dimethyl-silyloxy)-but-3-enyloxy]-2-chloro-benzonitrile. ^1H NMR (CDCl_3) δ 7.55 (m, 2H), 7.02 (m, 2H), 5.91-5.78 (m, 2H), 5.42-5.22 (m, 4H), 4.75 (m, 1H), 4.51 (m, 1H), 3.90 (m, 2H), 3.79 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.04 (s, 6H).

20

25

30

Step C: 2-Chloro-4-(1-hydroxymethyl-allyloxy)-benzonitrile

To a solution of the regioisomer mixture above, Example 31, Step B, (1.67 g, 4.95 mmol) in THF (15 mL) was added tert-butyl ammonium fluoride (1.0M in THF, 5.44 mL, 5.44 mmol). The reaction was stirred at room temperature for 15 minutes, was diluted with aqueous NH_4Cl and extracted with EtOAc (3x). The organic solution was washed with brine, dried (MgSO_4), filtered and concentrated. The residue was purified by medium pressure chromatography eluting with a solvent gradient (hexanes to 100% EtOAc in hexanes over 70 minutes) to provide 112 mg of 2-chloro-4-(1-hydroxymethyl-allyloxy)-benzonitrile. ^1H NMR (CDCl_3) δ 7.55 (d, 1H), 7.04 (d, 1H), 6.89 (dd, 1H), 5.85-5.76 (m, 1H), 5.38 (m, 2H), 4.80 (m, 1H), 3.80 (m, 2H).

-30-

EXAMPLE 31 A

This Example further illustrates the preparation of (1S,4S)-4-(4-hydroxy-1-methylpentoxy)-2-trifluoromethyl-benzonitrile, the product of Example 23.

5

NaH (60% in mineral oil) was suspended in 100 ml of dry THF, it was stirred and cooled to 0°C under N₂ for 10 min before adding the (2S,5S)-(+)-2,5-hexanediol (12.g in 120 ml of dry THF). The diol was added drop wise through a dropping funnel over 30 min., this mixture was stirred at 0°C for 60 min, then RT 30 min., it was re-cooled to 0°C before adding the 4-fluoro-2-(trifluoromethyl)benzonitrile (20g in 80 ml of dry THF) over 30 min. The reaction was then stirred at 0°C to RT under N₂ (11am-9am the next day). The reaction was monitored by TLC (Hex:Ethyl acetate=1:1) and LC/MS.

10

15

Purification: The crude product was dissolved in 80 ml of mixture solvent (hexane:ethyl acetate=3:1), column purification using hexane :ethyl acetate=5:1 to 1:1 as the elute to yield 22 g of the pure desired product.

20

EXAMPLE 32

The compounds of Formula I have affinity for the androgen receptor. This affinity has been demonstrated for selected compounds using the human androgen receptor. The description below describes how the assay was carried out.

25

Competitive binding analysis was performed on baculovirus/Sf9 generated hAR extracts in the presence or absence of different concentrations of test agent and a fixed concentration of ³H-dihydrotestosterone (³H-DHT) as tracer. This binding assay method is a modification of a protocol previously described (Liao S. , et. al. J. Steroid Biochem. 20:11-17 1984). Briefly, progressively decreasing concentrations of compounds are incubated in the presence of hAR extract (Chang et al. P.N.A.S. Vol. 89, pp. 5546-5950, 1992), hydroxylapatite, and 1 nM ³ H-DHT for one hour at 4°C. Subsequently, the binding reactions are washed three times to completely remove excess unbound ³ H-DHT. hAR bound ³H-DHT levels are determined in the presence of compounds (= i.e competitive binding)

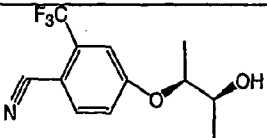
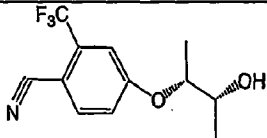
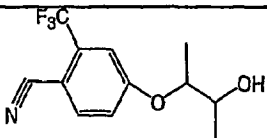
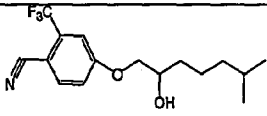
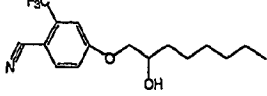
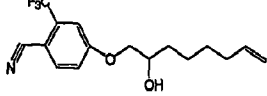
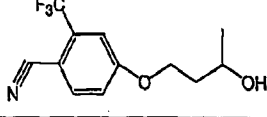
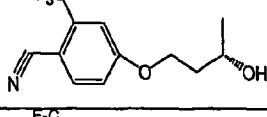
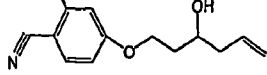
30

35

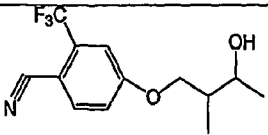
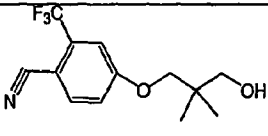
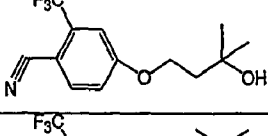
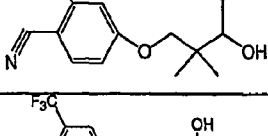
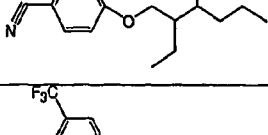
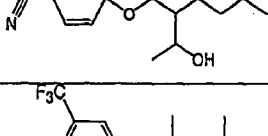
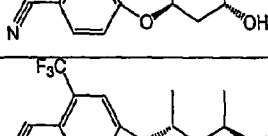
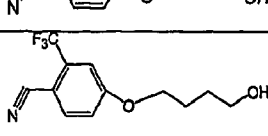
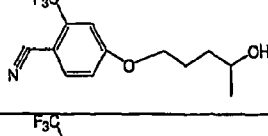
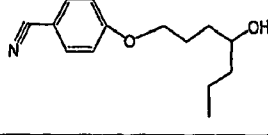
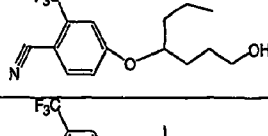
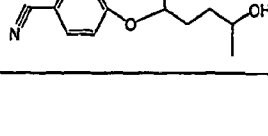

-31-

and compared to levels bound when no competitor is present (= i.e. maximum binding). Compound binding affinity to the hAR is expressed as the concentration of compound at which one half of the maximum binding is inhibited. Table II below provides the results that were obtained for selected compounds (reported data is the mean of multiple tests as shown below)

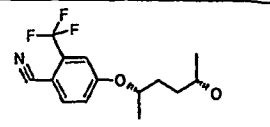
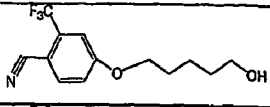
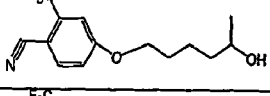
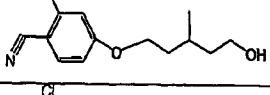
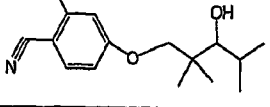
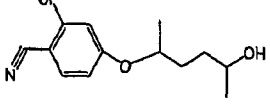
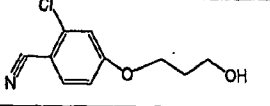
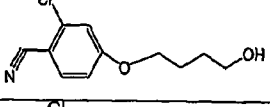
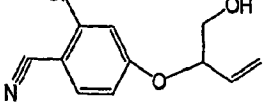
TABLE II

Example #	Structure	AR Binding IC ₅₀ (nM)
1		351 (c)
2		501 (c)
3		66 (b)
4		442 (a)
5		32 (a)
6		415 (a)
7		274 (a)
8		213 (a)
9		268 (a)

-32-

10		70 (a)
11		706 (a)
12		27 (a)
13		442 (a)
14		260 (b)
15		210 (a)
16		6 (a)
17		107 (a)
18		74 (a)
19		505 (a)
20		243 (a)
21		808 (a)
22		185 (a)

-33-

23		41 (c)
24		632 (c)
25		504 (a)
26		777 (a)
27		63 (c)
28		49 (a)
29		394 (a)
30		99 (a)
31		156 (a)

a – mean of two tests

b – mean of three tests

c – mean of four tests

EXAMPLE 33

5

The compounds ability to antagonize the effects of androgen on the androgen receptor were determined in a whole cell assay as described immediately below.

Experimental procedure for AR antagonist cell assay

10

Cell line: MDA-MB453-MMTV clone 54-19. This cell line is a stable transfected cell line with MDA-MB453 cell background (a human breast tumor cell line expressing androgen receptor). A MMTV minimal promoter containing ARE was

-34-

first cloned in front of a firefly luciferase reporter gene. Then the cascade was cloned into transfection vector pUV120puro. Electroporation method was used for transfecting MDA-MB-453 cell. Puromycin resistant stable cell line was selected.

5

Cell culture media and reagents:

Culture medium: DMEM (high glucose, Gibco cat #: 11960-044), 10%FBS, and 1% L-glutamine

10 **Plating medium:** DMEM (phenol red free), 10% charcoal treated HyClone serum, 1% L-glutamine

Assay medium: DMEM (phenol red free), 1% charcoal treated HyClone serum, 1% L-glutamine, and 1% penicillin/streptomycin

15 **3X luciferase buffer:** 2% beta-mercaptoethanol, 0.6% ATP, 0.0135% luciferine in cell lysis buffer

Assay procedure:

1. Cells are maintained in culture medium, splitting cells when they reach 80-90% confluence
- 20 2. To test compounds, 10,000 cells/well are plated to opaque 96 cell culture plate in 100 ul/well plating medium, culture for overnight at 37°C in cell culture incubator
3. Carefully remove plating medium, then add 80 ul/well of pre-warmed assay medium, add 10 ul/well testing compound (final concentration at) 1000 nM, 200 nM, 40 nM, 8 nM, 1.6 nM, and 0.32 nM), incubate at 37°C for 30 minutes
- 25 4. Add 10 ul/well freshly prepared DHT (final concentration at 100 pM) to each well, incubate at 37°C for 17 hr (overnight)
5. Add 50 ul/well 3X luciferase buffer, incubate at room temperature for 5 minutes, then count on Luminometer
- 30

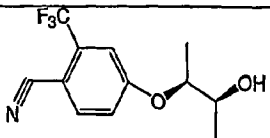
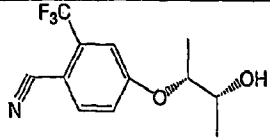
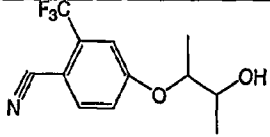
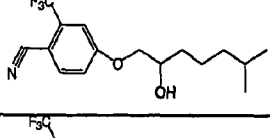
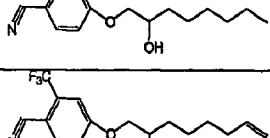
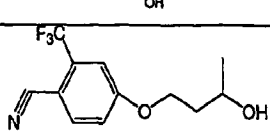
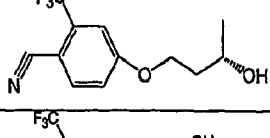
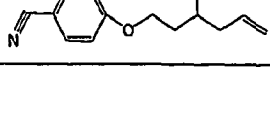

The fold induction over background by 100 pM DHT in the absence of testing compounds is standardized as 100% and experimental result is expressed as percentage of inhibition by testing compounds.

-35-

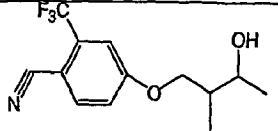
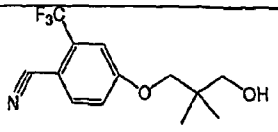
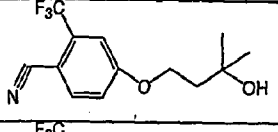
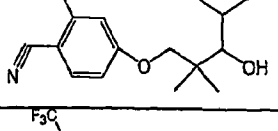
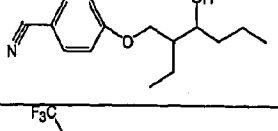
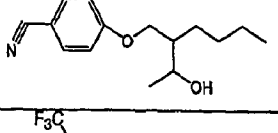
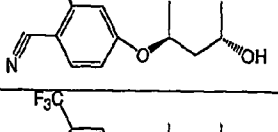
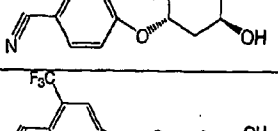
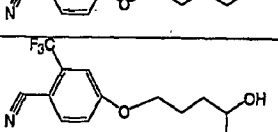
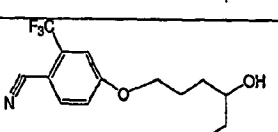
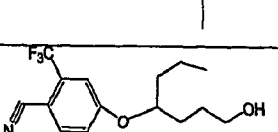
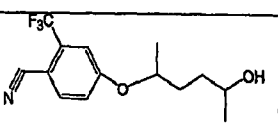

The results are described below in Table III. The results are reported as the mean of multiple tests as described below (the numbers of tests are indicated in the footnote). N.D. denotes that the compound was not tested.

5

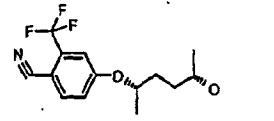
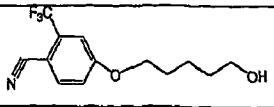

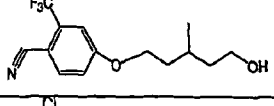
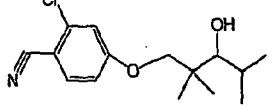
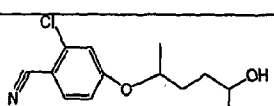
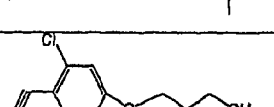
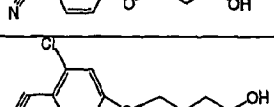
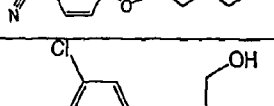
TABLE III

Example #	Structure	AR Cell IC50 (nM)
1		N.D.
2		N.D.
3		>1000 (a)
4		>1000 (a)
5		509 (a)
6		662 (a)
7		>1000 (c)
8		>1000 (a)
9		N.D.

-36-

10		274 (a)
11		N.D.
12		269 (a)
13		N.D.
14		794 (a)
15		124 (a)
16		>1000 (a)
17		807 (a)
18		398 (a)
19		>1000 (a)
20		498 (a)
21		N.D.
22		>1000 (a)

-37-

23		132 (N=10)
24		>1000 (a)
25		838 (N=1)
26		N.D.
27		0.04 (a)
28		263 (a)
29		N.D.
30		N.D.
31		N.D.

a – mean of two tests

b – mean of three tests

c – mean of four tests

5

EXAMPLE 34**Animal Model for Androgenetic Alopecia**

10

As described above, alopecia is a problem that medical science has devoted considerable resources to. As with any disease process, animal models have been developed to allow scientists to screen compounds for their potential relative efficacy. Those compounds showing the greatest efficacy in these animal models are considered for further study in humans. Two different animal models have been developed to date for alopecia. The first is the telogen conversion

-38-

assay, which uses female C3H/HeN mice. The second model uses stump-tailed macaques, which are monkeys that suffer from androgenetic alopecia.

5 The telogen conversion assay measures the potential of a compound to convert the resting stage of the hair growth cycle ("telogen") to the active stage of the hair growth cycle ("anagen") in mice. This assay takes advantage of the fact that the fur (i.e. hair) of 7-week-old C3H/HeN mice is in the telogen phase. This phase continues until about 75 days of age. In this assay, selected areas of the mice are shaved, contacted with a test agent, or a control, and the difference in the rate of hair growth is measured (i.e. induction of the anagen phase). The first
10 sign of anagen is the darkening of skin color as melanocytes in the follicles start to synthesize melanin, in preparation for the production of pigmented hairs. This model has a number of advantages. This includes the ready availability of female CH3HeN mice, the ability to screen large numbers of compounds quickly, and the ease of housing and handling such animals.

15 The primary disadvantage of this model is its lack of androgenetic dependency. While the exact cause of human baldness is not known, it is well documented that androgens induce a regression of hair follicles in the scalp. This post adolescent regressive change is a fundamental cause of male pattern baldness, (i.e. "androgenetic alopecia). This phenomenon occurs in both men
20 and women who have inherited the genetic trait for alopecia, as mentioned previously. For a more detail discussion of the effects of androgens on human scalps, the readers attention is directed to Trueb, RM, Molecular Mechanisms of Androgenic Alopecia, Exp. Gerontology, 2002, 27:981-990.

25 Researchers looked for other animals whose hair growth was similar to that of humans. These lead researchers to stump-tailed macaques. These primates also suffer from androgenetic alopecia. Essentially all post adolescent macaques, in both sexes, exhibit the development of baldness. Like the development of male pattern baldness in humans, androgens are an
30 indispensable triggering factor in macaque baldness. Thinning of the frontal scalp hairs begins to appear around the same age (4 years) when serum levels of testosterone become drastically elevated in male animals. Although the elevation of testosterone in females is approximately one tenth that of the male level, there

-39-

is no difference in the incidence and the age of onset of baldness between male and female stump-tailed macaques. Topical application of anti-androgens have reversed this baldness in animals of both sexes (Pan, H J et al, Evaluation of RU58841 as an anti-androgen in prostate PC3 cells and a topical anti-alopecia agent in the bald scalp of stump tailed macaques. Endocrine 1998; 9:39-43).

While this model is a significant improvement over the telogen conversion assay as a model for human baldness, it suffers from a number of practical disadvantages. The macaques are expensive, relatively rare, labor intensive to maintain, and require long wash out periods between testing. Thus, the macaque is not a practical model for screening large numbers of compounds

It has been discovered that male C3H/HeN mice may be used in the telogen conversion assay, when evaluating anti-androgen test compounds. Thus, the model relates to a modification of the existing telogen conversion assay. Male C3H/HeN mice approximately 7 weeks old are utilized. These animals are also uniformly in telogen, like their female counterparts. However, once shaven, the androgens inherently present in these male mice inhibit the conversion of the hair follicles to the anagen phase. An anti-androgen will block this androgenic effect and the follicles will convert to anagen, like their female counterparts.

Example 34A

The compound described in Example 23, (1S,4S)-4-(4-Hydroxy-1-methyl pentyloxy)-2-trifluoromethyl-benzonitrile was submitted for further testing utilizing the modified telogen conversion assay, described above. The testing was carried out in the following manner.

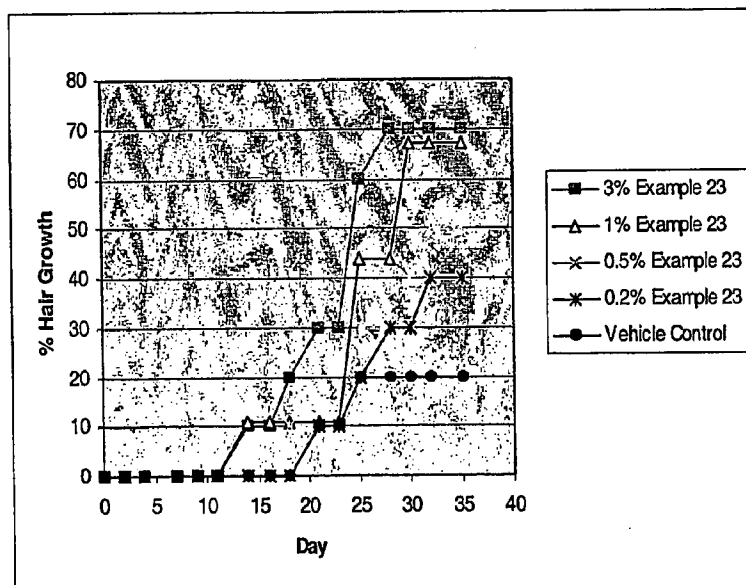
Male C3H/HeN mice, 6 to 7 weeks old (Charles River Laboratories, Raleigh, NC) were used for the study. Fur was clipped from the dorsal region of the mice prior to initiation of the study. Only mice with pink skin, a visual indication of the telogen phase, were selected for inclusion in the study.

The test compound was dissolved in a vehicle consisting of propylene glycol (30%) and ethanol (70%) to achieve a concentration of either 0.2% w/v, 0.5% w/v, 1% w/v or 3% w/v. The relevant dose was applied topically to the

-40-

clipped dorsal region of the mice in one test group (7-10 mice) in a volume of 20 $\mu\text{l}/\text{cm}^2$. A third group of animals received only the vehicle to serve as a control. Treatments were applied twice daily for 4 weeks.

- 5 The treatment area was observed and graded every other day for signs of hair growth. The hair growth response was quantified by recording, for each animal, the day on which signs of hair growth first appeared over the treated area. The first sign of anagen was the darkening of skin color as melanocytes in the follicles started to synthesize melanin in preparation for the production of pigmented hairs. The mice were observed for 35 days or longer. The percentage of mice showing signs of hair growth in both the treatment group and the control group is graphically depicted below in Figure I. The compound of Example 23, when tested at a concentration of 1%, produced substantial hair growth by stimulating the induction of anagen in the test animals. The rate of hair growth in the 5% test group did not exceed that of the vehicle control group.



20

Example 34 B

The product of Example 27, 2-chloro-4-(3-hydroxy-2,2,4-trimethyl-pentyloxy)-benzonitrile, was submitted for testing utilizing the modified telogen conversion assay, described above. The testing was carried out in the same

-41-

manner as Example 37 A, at a test concentration of 3 % w/v. The rate of hair growth for the test group did not exceed that of the vehicle control.

5

Example 35

Animal Model for Inhibition of Sebum Production

Luderschmidt et al describes an animal model for testing whether compounds are capable of modulating sebum secretion. Arch. Derm. Res. 258, 185-191 (1977). This model uses male Syrian hamsters, whose ears contain sebaceous glands. Selected compounds produced above were screened in this model.

Testing for sebum inhibition was carried out in the following manner. Male Syrian hamsters aged 9 to 10 weeks were introduced into the laboratory environment and acclimated for 2 weeks prior to use in the study. Each group consisted of 5 animals and were run in parallel with vehicle and positive controls. Prior to administration, 30mg of each compound was dissolved in 1 mL of Universal solvent (ethanol/ propylene glycol (70/30%v/v) to achieve a final concentration of 3 w/v%.

20

Animals were dosed topically twice daily, five days a week, for 4 weeks. Each dose consisted of 25 micro liters of vehicle control or drug. The dose was applied to the ventral surfaces of both the right and left ears. All animals were sacrificed approximately 18-24 hours after the final dose. The right ears were collected from each animal and used for sebum analysis.

25

The ears were prepped for HPLC analysis in the following manner. One 8mm distal biopsy punch was taken, just above the anatomical "V" mark in the ear to normalize the sample area. The punch was pulled apart. The ventral biopsy surface (the area where the topical dose was directly applied to the sebaceous glands) was retained for testing and the dorsal surface of the biopsy punch was discarded.

30

Tissue samples were blown with N₂ gas and stored at -80°C under nitrogen until HPLC analysis. In addition to ear samples, an aliquot of each drug

35

-42-

and vehicle (at least 250ul) was also stored at -80°C for inclusion in the HPLC analysis.

5 HPLC analysis was carried out on an extract of the tissue sample. Tissue samples were contacted with 3ml of solvent (a 4:1 admixture of 2,2,4-trimethylpentane and isopropyl alcohol). The mixture was shaken for 15 minutes and stored overnight at room temperature, protected from light. The next morning 1 milliliter of water was added to the sample and shaken for 15 minutes. The sample was then centrifuged at approximately 1500rpm for 15 minutes. Two
10 ml of the organic phase (top layer) was transferred to a glass vial, dried at 37°C, under nitrogen, for approximately 1 hour, and then lyophilized for approximately 48 hours. The samples were then removed from the lyophilizer and each vial was reconstituted with 600µl of solvent A (trimethylpentane/tetrahydrofuran (99:1). The samples were then recapped and vortexed for 5 minutes.

15

200µl of each sample was then transferred to a pre-labeled 200µl HPLC vial with 200 µL glass inserts. The HPLC vials were placed in the autosampler tray for the Agilent 1100 series HPLC unit. The Agilent 1100 HPLC system consisted of a thermostated autosampler, a quaternary pump, a column heater,
20 and an A/D interface module. All components were controlled by Agilent ChemStation software. A Waters Spherisorb S3W 4.6x100 mm analytical column was maintained at 30°C by the Agilent column heater unit. The HPLC autosampler was programmed to maintain the sample temperature at 20°C throughout the run.

25

10uL of each sample was injected in triplicate into the column. Two solvents were used for the solvent gradient. Solvent A was an admixture of trimethylpentane and tetrahydrofuran (99:1). Solvent B was ethylacetate. The gradient utilized is described in the table below:

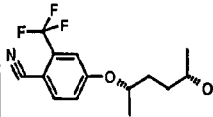
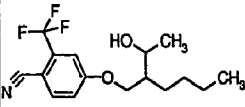
-43-

Time (min)	Solv A (%)	Solv B (%)	Flow (mL/min)
0	99	1	2
2	96	4	2
6	60	40	2
7	5	95	2
10	5	95	2
10.1	99	1	2

5 The Sedex 75 Evaporative Light Scattering Detector (ELSD) was
 operated at 45°C with a gain of 5, and N₂ pressure maintained at 3.1 bar. Analog
 signal obtained by the instrument was sent to the Agilent A/D interface module
 where it was converted to a digital output. The conversion was based on a
 10000 mAU/volt set point and the data rate was set at 10Hz (0.03 min). The
 resulting digital output was then feed into the Agilent ChemStation software for
 10 integration of the peak area.

The results of the HPLC analysis are reported below in Table IV. The
 results are reported as the reduction in cholesterol ester (CE) and wax ester (WE)
 production, when compared to the vehicle control.

15

Compound	Structure	% Reduction in CE	% Reduction in WE	Sum CE+WE
Example 23		67%	87%	154%
Example 15		54%	74%	128%

-44-

Columns 1 and 2 identify the compound by structure and Example number.

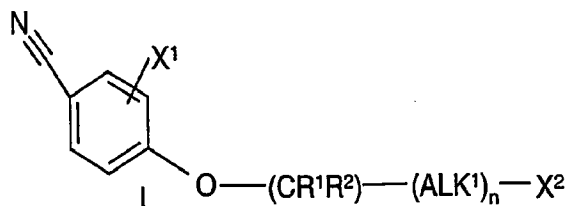
Columns 3 through 5 show the effect the compounds had on the -reduction of sebum components (CE and WE). The results are expressed as the difference from the vehicle control. A positive number reflects a decrease in the production of the sebum component being measured, i.e. cholesterol ester (CE) or wax ester (WE).

Column 3 shows the compounds ability to reduce the amount of cholesterol ester in the sebum sample. Column 4 shows the effect the compound had on the generation of wax ester. Wax esters are specific markers of the sebaceous glands and are not appreciably detected in any other layer of the skin. Wax ester is the largest component of sebum (approximately 25%). Thus reducing wax ester typically leads to significant reductions in sebum secretion. Column 5 is a summation of the results expressed in columns 3 and 4 (and is included to further elucidate relative differences in activity). As shown in Table IV, the androgen modulators of Formula I significantly decreased the production of both cholesterol ester and wax ester.

-45-
CLAIMS

What is claimed is:

1. A compound of the formula:



5

a prodrug of said compound, a hydrate of said compound or a pharmaceutically acceptable salt of said compound, in which:

10

X¹ is represented by halogen or haloalkyl;

X² is represented by -CR³R⁴R⁵, -CH=CH₂, or -C≡CH;

R¹, and R², are each independently represented by a substituent selected from the group consisting of hydrogen, C₁-₆ alkyl, halogen, haloalkyl, hydroxyalkyl, thiol, and thioalkyl;

15

R³, R⁴, and R⁵ are each independently represented by a substituent selected from the group consisting of hydrogen, halogen, C₁-₆ alkyl, haloalkyl, hydroxy, hydroxyalkyl, thiol, thioalkyl and -NR⁶R⁷;

n is represented by 0 or 1;

20

ALK¹ is represented by a C₁-₈ linear alkylene group, in which up to 8 hydrogen atoms of the alkylene group may optionally be replaced by a substituent selected from the group consisting of C₁-₈ alkyl, haloalkyl, halogen, hydroxy, hydroxyalkyl, thiol, and thioalkyl and -NR⁶R⁷;

R⁶ and R⁷ are each independently represented by hydrogen or C₁-₆ alkyl; with the proviso that:

25

- 1) if n is 0 and X² is represented by -CH=CH₂ or -C≡CH, then at least one of R¹ or R² is represented by thiol, hydroxyalkyl, or thioalkyl;
- 2) if n is 1 and X² is represented by -CH=CH₂ or -C≡CH, then alternatively, at least one of R¹ or R² is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl,

-46-

or at least one hydrogen atom from Alk^1 is replaced by a substituent selected from the group consisting of hydroxy, thiol, hydroxyalkyl, and thioalkyl;

3) if n is 0 and X^2 is represented by $-\text{CR}^3\text{R}^4\text{R}^5$, then, in the alternative, at least one of R^1 or R^2 is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl, or at least one of R^3 , R^4 , or R^5 is represented by hydroxy, hydroxyalkyl, thiol, or thioalkyl;

4) if n is 1 and X^2 is represented by $-\text{CR}^3\text{R}^4\text{R}^5$, then alternatively: a) at least one of R^1 or R^2 is represented by a substituent selected from the group consisting of thiol, hydroxyalkyl, and thioalkyl, b) at least one of R^3 , R^4 , or R^5 is represented by a substituent selected from the group consisting of hydroxy, hydroxyalkyl, thiol, and thioalkyl; or c) at least one hydrogen atom of Alk^1 is replaced with a substituent selected from the group consisting of hydroxy, thiol, thioalkyl, and hydroxyalkyl.

2. A compound according to claim 1 in which n is 0 and at least one of R^1 , R^2 , R^3 , R^4 , R^5 is represented by C_{1-6} alkyl, haloalkyl, hydroxyalkyl, and thioalkyl.

3. A compound according to claim 1, in which n is 1, and at least one hydrogen atom from Alk^1 has been replaced by a substituent selected from the group consisting of C_{1-6} alkyl, haloalkyl, hydroxyalkyl, and thioalkyl, or one of R^1 , R^2 , R^3 , R^4 , R^5 is represented by C_{1-6} alkyl, haloalkyl, hydroxyalkyl, and thioalkyl.

4. A compound according to claim 1, 2, or 3 in which X^1 is CF_3 and is located at the 2-position of the phenyl ring.

5. A compound according to claim 1, 2, 3, or 4 in which X^2 is $\text{CR}^3\text{R}^4\text{R}^5$, in which at least one of R^3 , R^4 , or R^5 is hydroxy or hydroxyalkyl.

6. A compound according to claim 5 in which at least one of R^3 , R^4 , or R^5 is methyl.

7. A compound according to claim 1 in which said compound is selected from the group consisting of:

(1S,2S)-4-(2-hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile;

(1R,2R)-4-(2-hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile;

4-(2-hydroxy-1-methyl-propoxy)-2-trifluoromethyl-benzonitrile;

-47-

- 4-(2-hydroxy-6-methyl-heptyloxy)-2-trifluoromethyl-benzonitrile;
 4-(2-hydroxy-octyloxy)-2-trifluoromethyl-benzonitrile;
 4-(2-hydroxy-oct-7-enyloxy)-2-trifluoromethyl-benzonitrile;
 4-(3-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
 5 (3S)-4-(3-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
 4-(3-hydroxy-hex-5-enyloxy)-2-trifluoromethyl-benzonitrile;
 4-(3-hydroxy-2-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
 4-(3-hydroxy-2, 2-dimethyl-propoxy)-2-trifluoromethyl-benzonitrile;
 4-(3-hydroxy-3-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
 10 4-(3-hydroxy-2,2,4-trimethyl-pentyloxy)-2-trifluoromethyl-benzonitrile;
 4-(2-ethyl-3-Hydroxy-hexyloxy)-2-trifluoromethyl-benzonitrile;
 4-[2-(1-hydroxy-ethyl)-hexyloxy]-2-trifluoromethyl-benzonitrile;
 (1S,3S)-4-(3-hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
 (1R,3R)-4-(3-hydroxy-1-methyl-butoxy)-2-trifluoromethyl-benzonitrile;
 15 4-(4-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
 4-(4-hydroxy-butoxy)-2-trifluoromethyl-benzonitrile;
 4-(4-hydroxy-heptyloxy)-2-trifluoromethyl-benzonitrile;
 4-(4-hydroxy-1-propyl-butoxy)-2-trifluoromethyl-benzonitrile;
 4-(4-hydroxy-1-methyl-pentyloxy)-2-trifluoromethyl-benzonitrile;
 20 (1R,4R)-4-(4-hydroxy-1-methyl-pentyloxy)-2-trifluoromethyl-benzonitrile;
 (1S,4S)-4-(4-hydroxy-1-methyl-pentyloxy)-2-trifluoromethyl-benzonitrile
 4-(5-hydroxy-pentyloxy)-2-trifluoromethyl-benzonitrile;
 4-(5-hydroxy-hexyloxy)-2-trifluoromethyl-benzonitrile;
 4-(5-hydroxy-3-methyl-pentyloxy)-2-trifluoromethyl-benzonitrile;
 25 2-chloro-4-(3-Hydroxy-2,2,4-trimethyl-pentyloxy)-benzonitrile;
 2-chloro-4-(4-Hydroxy-butoxy)-benzonitrile;
 2-chloro-4-(3-Hydroxy-propoxy)-benzonitrile;
 2-chloro-4-(1-Hydroxymethyl-allyloxy)-benzonitrile;
 2-chloro-4-(3-Hydroxy-2-methyl-propoxy)-benzonitrile
 30 2-chloro-4-(5-Hydroxy-pentyloxy)-benzonitrile;
 2-chloro-4-(4-Hydroxy-1-methyl-pentyloxy)-benzonitrile, and;
 2-chloro-4-(5-Hydroxy-3-methyl-pentyloxy)-benzonitrile.
8. (1S,4S)-4-(4-Hydroxy-1-methyl-pentyloxy)-2-trifluoromethyl-benzonitrile,
 35 or a pharmaceutically acceptable salt, thereof.

-48-

9. Use of a compound according to anyone of claims 1-8 as a medicine.
10. Use of a compound according to anyone of claims 1-8 in the manufacture of a medicament for modulating activation of the androgen receptor.
- 5 11. Use of a compound according to any one of claims 1-8 in the manufacture of a topical medicament for androgenetic alopecia, excess sebum or acne.
- 10 12. A pharmaceutical composition comprising a compound according to anyone of claims 1-8 in admixture with 1, or more, pharmaceutically acceptable excipients.
- 15 13. A topical pharmaceutical formulation comprising a compound according to anyone of claims 1-8 in admixture with 1, or more, pharmaceutically acceptable excipients suitable for dermal application.
- 20 14. An article of manufacture comprising a compound according to anyone of claims 1-8 packaged for retail distribution which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.

25

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C255/54 A61K31/277 A61P5/28 A61P17/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/08673 A (BRISTOL-MYERS SQUIBB COMPANY) 25 February 1999 (1999-02-25) claims 3,7	1-14
A	DE 102 18 963 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH) 20 November 2003 (2003-11-20) claims 1-14	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

5 July 2005

Date of mailing of the international search report

01/08/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Goetz, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern.

Application No

PCT/IB2005/000229

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9908673	A	25-02-1999	AU 736687 B2	02-08-2001
			AU 8680898 A	08-03-1999
			BR 9811485 A	19-09-2000
			CA 2300414 A1	25-02-1999
			CN 1265589 A	06-09-2000
			EP 1003502 A1	31-05-2000
			HU 0003417 A2	28-02-2001
			ID 24267 A	13-07-2000
			JP 2001515034 T	18-09-2001
			NO 20000686 A	31-03-2000
			NZ 502125 A	31-08-2001
			PL 338668 A1	20-11-2000
			TR 200000343 T2	21-08-2000
			WO 9908673 A1	25-02-1999
			US 6013668 A	11-01-2000
			US 6472427 B1	29-10-2002
			US 6262122 B1	17-07-2001
			US 2001020038 A1	06-09-2001
			ZA 9807220 A	14-02-2000
DE 10218963	A1	20-11-2003	AU 2003229658 A1	17-11-2003
			BR 0309579 A	01-03-2005
			CA 2483786 A1	13-11-2003
			WO 03093243 A1	13-11-2003
			EP 1501806 A1	02-02-2005
			US 2003229129 A1	11-12-2003

10



Europäisches Patentamt

European Patent Office

Office européen des brevets

11 Publication number:

**0 100 172
B1**

12

EUROPEAN PATENT SPECIFICATION

45 Date of publication of patent specification: 12.08.87

21 Application number: 83303998.5

72 Date of filing: 08.07.83

51 Int. Cl.⁴: **C 07 C 149/23**,
C 07 C 149/41,
C 07 C 103/375,
C 07 C 103/50, C 07 C 121/78,
C 07 C 147/107,
C 07 C 147/14,
C 07 D 213/70,
C 07 D 247/02,
C 07 D 283/02, C 07 D 285/12

54 Amide derivatives.

20 Priority: 23.07.82 GB 8221421

43 Date of publication of application:
08.02.84 Bulletin 84/06

45 Publication of the grant of the patent:
12.08.87 Bulletin 87/33

64 Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

50 References cited:
EP-A-0 002 309
EP-A-0 002 892
EP-A-0 040 932
FR-A-2 142 803
US-A-3 133 119

70 Proprietor: **IMPERIAL CHEMICAL INDUSTRIES
PLC**
Imperial Chemical House Millbank
London SW1P 3JF (GB)

72 Inventor: Tucker, Howard
32 Millers Meadow
Rainow Macclesfield Cheshire (GB)

74 Representative: Slatcher, Reginald Peter et al
Imperial Chemical Industries PLC Legal
Department: Patents PO Box 6
Welwyn Garden City Herts, AL7 1HD (GB)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

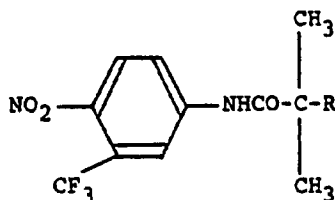
Courier Press, Leamington Spa, England.

EP 0 100 172 B1

Description

This invention relates to new amide derivatives and more particularly it relates to novel acylanilides which possess antiandrogenic properties.

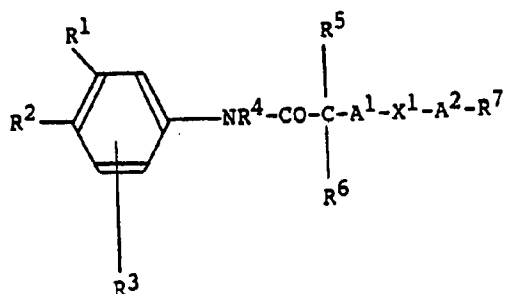
Many acylanilides are known which possess antiandrogenic activity. In particular, the compound of the formula:—



wherein R is hydrogen, which compound is known as FLUTAMIDE, is under development for use as an antiandrogen. It is believed that flutamide is oxidised *in vivo* to the corresponding compound wherein R is hydroxy.

Other acylanilides which possess antiandrogenic activity are known from European Specification Nos. 2309, 2892 and 40932, and from Japanese Specification No. 52—128329.

According to the present invention there is provided an acylanilide of the formula:—



wherein R¹ is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R² is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R³ is hydrogen or halogen;

wherein R⁴ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R⁵ as stated below;

wherein R⁶ is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R⁴ to form an oxycarbonyl group such that together with the —N—CO—C— part of the molecule it forms an oxazolidinedione group;

wherein R⁶ is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula —A³—R⁸ or —A⁴—X²—A⁵—R⁹;

wherein A¹ and A⁴, which may be the same or different, each is alkylene of up to 6 carbon atoms;

wherein A², A³ and A⁵, which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X¹ and X², which may be the same or different, each is sulphur, sulphanyl (—SO—) or sulphonyl (—SO₂—);

wherein R⁷ and R⁹, which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R⁷ or R⁹ is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R⁷ or R⁹ is naphthyl; or R⁷ or R⁹ is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R⁸ is phenyl, naphthyl or heterocyclic as defined above for R⁷ or R⁹.

It will be observed that the acylanilide derivative of the invention possesses an asymmetric carbon atom, namely the carbon atom which bears the substituents R^5 and R^6 , and it can therefore exist in racemic and optically-active forms. It is to be understood that this invention encompasses the racemic form of the acylanilide derivative and any optically-active form which possesses antiandrogenic activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any antiandrogenic activity present in any of these forms may be determined.

A suitable value for R^1 , R^4 or R^{10} when it is alkyl, or for an alkyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by alkyl is, for example, methyl or ethyl.

A suitable value for R^1 when it is alkoxy, or for an alkoxy substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for R^1 or R^2 when it is alkanoyl, or for an alkanoyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl substituted by alkanoyl is, for example, formyl or acetyl.

A suitable value for R^1 or R^2 when it is alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl, or for such a substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic bearing such a substituent is, for example, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for R^3 when it is halogen, or for a halogen substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by halogen, is fluoro, chloro, bromo or iodo.

R^3 is preferably hydrogen or chloro, especially hydrogen.

R^4 is preferably hydrogen.

A suitable value for an alkoxycarbonyl or *N*-alkylcarbamoyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl bearing such a substituent is, for example, methoxycarbonyl, ethoxycarbonyl or *N*-methylcarbamoyl.

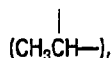
A suitable value for R^5 when it is alkoxy is, for example, methoxy, ethoxy, propyloxy, *n*-butyloxy or decyloxy.

A suitable value for R^5 when it is acyloxy is, for example, alkanoyloxy or aroyloxy each of up to 15 carbon atoms, for example acetoxo, propionyloxy, decanoyloxy, dodecanoyloxy or benzoyloxy.

R^5 is preferably hydroxy.

A suitable value for R^6 when it is alkyl or halogenoalkyl is, for example, methyl, ethyl, *n*-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, chloromethyl, dichloromethyl or trichloromethyl. R^6 is preferably methyl or trifluoromethyl, especially methyl.

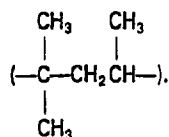
A suitable value for A^1 , A^2 , A^3 , A^4 or A^5 when it is alkylene is, for example, methylene, ethylene, ethylidene



trimethylene, tetramethylene, 1-methyl-ethylene



or 1,1,3-trimethylpropane-1,3-diyl



A suitable value for R^7 or R^9 when it is alkyl, alkenyl, hydroxyalkyl or cycloalkyl is, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, allyl, 2-methylprop-2-enyl, 2-hydroxyethyl, cyclopentyl or cyclohexyl.

A suitable value for R^7 , R^8 or R^9 when it is heterocyclic is, for example, furyl, thienyl, pyrrolyl, pyridyl, imidazolyl, thiazolyl, pyrimidinyl, thiadiazolyl, triazolyl, benzimidazolyl, benzothiazolyl, indolyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or 1,2-dihydro-2-oxoquinolyl.

A preferred combination of values for R^1 and R^2 is as follows:—

R ¹	R ²
trifluoromethyl	nitro
trifluoromethyl	cyano
chloro	chloro
chloro	nitro
chloro	cyano
cyano	cyano

A preferred acylanilide of the invention has the formula stated above wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphinyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent.

A particularly preferred acylanilide of the invention has the formula stated above wherein R¹ is trifluoromethyl, R² is cyano or nitro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur, sulphinyl or sulphonyl, A² is a direct link and R⁷ is alkyl of up to 3 carbon atoms, especially ethyl, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

Specific acylanilides of the invention are hereinafter described in the Examples.

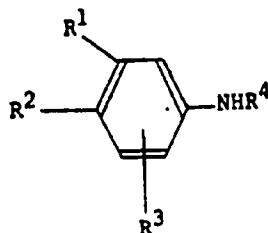
Particularly active compounds are:

3-chloro-4-cyano-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)aniline;
 3-chloro-4-cyano-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylsulphonyl-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 3-chloro-4-nitro-*N*-(2-hydroxy-3-phenylthio-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-allylthio-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylsulphonyl)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-methylthiopropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline; and
 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;

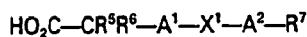
and of these the last-mentioned is especially preferred.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

One preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:—

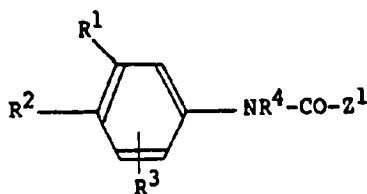


wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above, with an acid of the formula:—

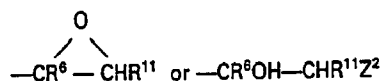


wherein R^5 , R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, or with a reactive derivative of said acid.
A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester. Preferably the reaction is carried out in *N,N*-dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

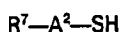
A second preferred process for the manufacture of an acylanilide of the invention wherein R^5 is hydroxy and X^1 is sulphur comprises the reaction of an epoxide of the formula:—



wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above and wherein Z^1 has the formula



wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $-CHR^{11}-$ is $-A^1-$ as stated above, with a thiol of the formula:—

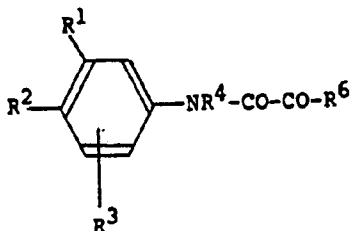


wherein R^7 and A^2 have the meanings stated above.

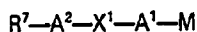
A suitable value for Z^2 is, for example, a halogeno or sulphonyloxy group, for example the chloro, bromo, iodo, methanesulphonyloxy or *p*-toluenesulphonyloxy group. The abovementioned reaction is preferably carried out in an inert diluent or solvent, for example tetrahydrofuran, and in the presence of a base, for example sodium hydride.

The epoxide used as starting material may be obtained by the epoxidation, for example with a peracid, of the corresponding unsaturated acylanilide.

A third preferred process for the manufacture of an acylanilide of the invention wherein R^5 is hydroxy comprises the reaction of a compound of the formula:—



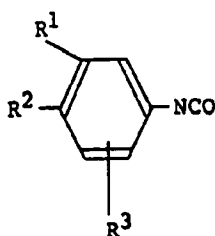
wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings stated above, with an organometallic compound of the formula —



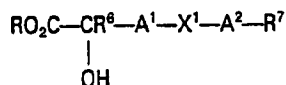
wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical, for example the lithium radical.

The last-mentioned reaction is preferably carried out in an inert solvent, for example diethyl ether or tetrahydrofuran, at a low temperature, for example at between -60°C and -100°C .

An acylanilide of the invention wherein R^4 and R^5 are joined together to form a carbonyloxy group, that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:—



wherein R¹, R² and R³ have the meanings stated above, with an ester of the formula:—



wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

An acylanilide of the invention wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy, and an acylanilide of the invention wherein R⁵ is hydroxy and R⁴ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in the preceding paragraph.

An acylanilide of the invention wherein R⁴ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R⁴ is hydrogen.

An acylanilide of the invention wherein R⁵ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R⁵ is hydroxy.

An oxazolidinedione of the invention, wherein R⁴ and R⁵ are joined together to form a carbonyloxy group, may be prepared by the reaction of the corresponding acylanilide wherein R⁴ is hydrogen and R⁵ is hydroxy with phosgene (COCl₂).

An acylanilide of the invention wherein X¹ or X² is sulphinyl or sulphonyl or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein X¹ or X² is sulphur or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or a sulphonyl compound is obtained. Thus, oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with a per-acid, for example *m*-chloroperbenzoic acid, in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

A racemic acylanilide of the invention wherein R⁵ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, for example (–)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallisation or, preferably, by flash-chromatography, and then hydrolysing each separate ester to the alcohol. Alternatively, an optically active acylanilide of the invention may be obtained by using any of the processes described above with an optically-active starting material.

As stated above, an acylanilide of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles of a mature male rat when administered orally for 4 successive days. An acylanilide of the invention may therefore be used in the treatment of, for example, malignant or benign prostatic disease or of androgen dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

A preferred acylanilide of the invention is up to 10 times more active as an antiandrogen than the known, chemically-related antiandrogens flutamide and hydroxyflutamide. At a dose of an acylanilide of the invention which produces antiandrogenic activity in rats no symptoms of toxicity are apparent.

The acylanilide of the invention may be administered to a warm-blooded animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration, or be in the form of a suppository for anal or vaginal administration.

The composition may additionally contain one or more drugs selected from anti-oestrogens, for example tamoxifen; aromatase inhibitors, for example testolactone or aminoglutethamide; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol;

LH—RH-analogues, for example busserelin; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide.

The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:—

Example 1

Thionyl chloride (0.6 ml.) was added to a stirred solution of 2-hydroxy-2-methyl-3-phenylthiopropionic acid (1.7 g) in *N,N*-dimethylacetamide (40 ml.) which was cooled to $-15^{\circ}\text{C}.$, at such a rate that that temperature was maintained, and the mixture was stirred at that temperature for 15 minutes. 4-Cyano-3-trifluoromethylaniline (1.5 g.) was added, the mixture was stirred at $-15^{\circ}\text{C}.$ for 30 minutes and then at laboratory temperature for 15 hours, and was then poured into water (800 ml.). The mixture was extracted six times with diethyl ether (80 ml. each time) and the combined extracts were washed successively (50 ml. portions each time) twice with aqueous 3N-hydrochloric acid, once with saturated aqueous sodium chloride solution, twice with saturated aqueous sodium bicarbonate solution, and again once with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (Merck 7734) using methylene chloride as eluant. The product was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and there was thus obtained 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline, m.p. $81.5-83^{\circ}\text{C}.$

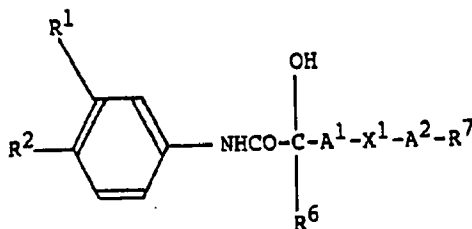
The 2-hydroxy-2-methyl-3-phenylthiopropionic acid used as starting material was obtained as follows:—

Route A

A solution of methyl 2,3-epoxy-2-methyl-propionate (4.06 g.) in tetrahydrofuran (40 ml.) was added during 20 minutes to a stirred suspension of thiophenol (7.7 g.) and sodium hydride (2.9 g. of a 60% dispersion in mineral oil) in tetrahydrofuran (75 ml.) which was maintained under an atmosphere of nitrogen, and the mixture was stirred at laboratory temperature for 15 minutes, then at $60^{\circ}\text{C}.$ for 4 hours, cooled and neutralised by dropwise addition of a solution of concentrated sulphuric acid (0.5 ml.) in ethanol (5 ml.). A solution of potassium hydroxide (10 g.) in a mixture of water (30 ml.) and ethanol (150 ml.) was added and the mixture was heated under reflux for 22 hours. The organic solvents were removed by evaporation under reduced pressure, water (50 ml.) was added and the mixture was washed twice with diethyl ether (25 ml. each time). The aqueous solution was then acidified with concentrated aqueous hydrochloric acid and extracted four times with diethyl ether (100 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution (50 ml.), dried over magnesium sulphate and evaporated to dryness, and the residue was crystallised from a 5:1 v/v mixture of petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and toluene. There was thus obtained 2-hydroxy-2-methyl-3-phenylthiopropionic acid, m.p. $95.5-97^{\circ}\text{C}.$

Example 2

The process described in Example 1 was repeated except that the appropriate aniline and the appropriate 2-hydroxy-substituted-alkanoic acid were used as starting materials. There was thus obtained the compounds described in the following table:—



R ¹	R ²	R ⁶	A ¹	X ¹	A ²	R ⁷	m.p. (°C)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	phenyl	105—106
CF ₃	NO ₂	CH ₃	CH ₂	S	—	2-nitrophenyl	52—54
CF ₃	NO ₂	CH ₃	CH ₂	S	—	methyl	109—110
CF ₃	NO ₂	CH ₃	CH ₂	S	—	ethyl	(gum)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	n-propyl	(gum)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	isopropyl	66—68
CF ₃	CN	CH ₃	CH ₂	S	—	ethyl	(gum)
CF ₃	CN	CH ₃	CH ₂	S	—	n-propyl	(gum)
CF ₃	CN	CH ₃	CH ₂	S	—	isopropyl	98—100
CF ₃	CN	CH ₃	CH ₂	S	—	methyl	108.5—109.5
CN	CN	CH ₃	CH ₂	S	—	phenyl	82—83.5
Cl	Cl	CH ₃	CH ₂	S	—	methyl	90.5—91.5
Cl	CN	CH ₃	CH ₂	S	—	phenyl	60—62
Cl	CN	CH ₃	CH ₂	S	—	ethyl	96—98
NO ₂	Cl	CH ₃	CH ₂	S	—	phenyl	77—78
Cl	NO ₂	CH ₃	CH ₂	S	—	phenyl	88—90
Cl	NO ₂	CH ₃	CH ₂	S	—	ethyl	(gum)
Cl	NO ₂	CH ₃	CH ₂	S	—	n-butyl	(gum)
CH ₃ O	CN	CH ₃	CH ₂	S	—	phenyl	(gum)
CH ₃	CN	CH ₃	CH ₂	S	—	phenyl	98—99
CF ₃	NO ₂	CH ₃	CH ₂	S	CH ₂	phenyl	79—80
CF ₃	NO ₂	CH ₃	CH ₂ CH ₂	S	—	phenyl	(gum)
CF ₃	CN	CH ₃	CH ₂ CH ₂	S	—	phenyl	115—116.5
CF ₃	CN	CH ₃	CH ₂	S	CH ₂	phenyl	105—106
Cl	CN	CH ₃	CH ₂	S	CH ₂	phenyl	123—124
CF ₃	NO ₂	CF ₃	CH ₂	S	—	phenyl	139—140
CF ₃	NO ₂	CF ₃	CH ₂	S	—	4-chlorophenyl	147—148
CF ₃	NO ₂	CF ₃	CH ₂	S	—	4-nitrophenyl	145—146
CF ₃	NO ₂	CF ₃	CH ₂	S	—	methyl	82—85
CF ₃	NO ₂	CF ₃	CH ₂	S	—	ethyl	79—81
CF ₃	NO ₂	CF ₃	CH ₂	S	—	n-propyl	67—68

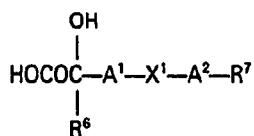
	R ¹	R ²	R ⁶	A ¹	X ¹	A ²	R ⁷	m.p. (°C.)
5	CF ₃	NO ₂	CF ₃	CH ₂	S	—	isopropyl	88—89
	CF ₃	CN	CF ₃	CH ₂	S	—	phenyl	143—144
	CF ₃	CN	CF ₃	CH ₂	S	—	4-chlorophenyl	178—179
10	CF ₃	CN	CF ₃	CH ₂	S	—	methyl	120.5—122
	CF ₃	CN	CF ₃	CH ₂	S	—	ethyl	119—120
	CF ₃	CN	CF ₃	CH ₂	S	—	n-propyl	88—90
15	CF ₃	CN	CF ₃	CH ₂	S	—	isopropyl	107—109
	Cl	Cl	CF ₃	CH ₂	S	—	phenyl	104
20	Cl	Cl	CF ₃	CH ₂	S	—	methyl	84—85
	Cl	Cl	CF ₃	CH ₂	S	—	ethyl	57—59
	Cl	Cl	CF ₃	CH ₂	S	—	n-propyl	60—61
25	Cl	Cl	CF ₃	CH ₂	S	—	isopropyl	57—59
	Cl	CN	CF ₃	CH ₂	S	—	phenyl	152
30	Cl	CN	CF ₃	CH ₂	S	—	methyl	121—122.5
	Cl	CN	CF ₃	CH ₂	S	—	ethyl	95—96
	Cl	CN	CF ₃	CH ₂	S	—	n-propyl	89—90
35	Cl	CN	CF ₃	CH ₂	S	—	isopropyl	87—88
	CF ₃	NO ₂	CF ₃	CH ₂	S	CH ₂	phenyl	120—121
40	CF ₃	CN	CF ₃	CH ₂	S	CH ₂	phenyl	138—139
	Cl	Cl	CF ₃	CH ₂	S	CH ₂	phenyl	145—146

45 All the anilines used as starting materials are known compounds. The 2-hydroxy-substituted-alkanoic acids were obtained either by the process described in the second part of Example 1 (Route A), or by the process exemplified below (Route B). Those acids which are novel and which were characterised by melting point are described in the table below:—

50 *Route B*

1,1,1-Trifluoro-3-phenylthioprop-2-one (13.1 g.) was added dropwise to a cooled stirred solution of potassium cyanide (4.4 g.) in water (16 ml.) at such a rate that the temperature of the mixture was maintained at between 0° and 5°C. A 4:1 v/v mixture of water and concentrated sulphuric acid (17.1 ml.) was added at such a rate as to maintain the above temperature, and the mixture was then stirred at laboratory temperature for 15 hours and then extracted three times with diethyl ether (25 ml. each time). The combined extracts were washed three times with water (25 ml. each time), dried over magnesium sulphate and evaporated to dryness under reduced pressure.

55 A mixture of the cyanhydrin thus obtained (3.0 g.) and concentrated aqueous hydrochloric acid (30 ml.) was heated in a sealed tube at 110°C. for 6 hours, cooled and poured onto ice. The aqueous mixture was extracted four times with diethyl ether (25 ml. each time) and the combined ethereal solutions were extracted twice with saturated aqueous sodium bicarbonate solution (40 ml. each time). The combined extracts were acidified with aqueous hydrochloric acid and then extracted twice with diethyl ether (40 ml. each time). The combined extracts were dried over magnesium sulphate and evaporated to dryness and the residue was stirred with petroleum ether (b.p. 60—80°C.). The mixture was filtered and there was thus
60 obtained as solid residue 2-hydroxy-3-phenylthio-2-trifluoromethylpropionic acid, m.p. 83—84°C.

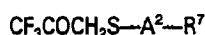


5

	R ⁶	A ¹	X ¹	A ²	R ⁷	Route	m.p. (°C)
10	CH ₃	CH ₂	S	—	2-nitrophenyl	B	85—88
	CH ₃	CH ₂	S	—	methyl	A	48—52
	CH ₃	CH ₂	S	—	isopropyl	A	50—52
15	CH ₃	CH ₂	S	CH ₂	phenyl	A	62—63
	CF ₃	CH ₂	S	—	4-nitrophenyl	B	169—171*
20	CF ₃	CH ₂	S	—	methyl	B	73—76
	CF ₃	CH ₂	S	—	n-propyl	B	37—40
	CF ₃	CH ₂	S	—	isopropyl	B	57—59
25	CF ₃	CH ₂	S	CH ₂	phenyl	B	91—92

*m.p. of dicyclohexylamine salt used for characterisation.

30 The thio-alkanones used in Route B were prepared by the reaction of the appropriate thiol with the appropriate bromoketone by conventional means (for example as described in Zhur.org.Khim., 1971, 7, 2221). Those which are novel and were characterised are described in the following table:—



35

40

45

A ²	R ⁷	b.p. (°C./mm.Hg.)
—	4-nitrophenyl	84.5—86 (m.p.)
—	methyl	39—47/100
—	n-propyl	72—82/65
—	isopropyl	75—85/87
CH ₂	phenyl	118—122/17

Example 3

50 A solution of ethanethiol (0.45 ml.) in tetrahydrofuran (5 ml.) was added dropwise to a stirred suspension of sodium hydride (0.28 g. of a 60% dispersion in mineral oil) in tetrahydrofuran (10 ml.) which was maintained at 0—5°C., and the mixture was then stirred at laboratory temperature for 15 minutes. A solution of 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline (1.5 g.) in tetrahydrofuran (15 ml.) was added dropwise and the mixture was stirred at laboratory temperature for 15 hours. Water (50 ml.) was added, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether (25 ml. each time). The combined organic solutions were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by flash-chromatography on silica gel (Merck 9385) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant. The product was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. 60—80°C.) and there was thus obtained 3,4-dichloro-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)aniline, m.p. 81—83°C.

55 The 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline used as starting material was obtained as follows:—

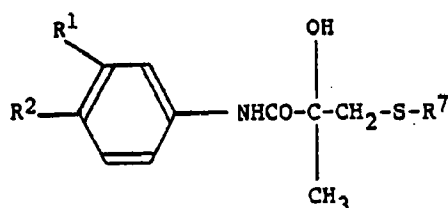
65 A solution of 3,4-dichloroaniline (10 g.) in dimethylacetamide (25 ml.) was added dropwise to a stirred, cooled solution of methacryloyl chloride (10 ml.) in dimethylacetamide (50 ml.) at such a rate that the internal temperature of the mixture did not exceed 0°C., and the mixture was then stirred at laboratory

temperature for 16 hours and then poured into cold water (1 litre). The mixture was extracted 5 times with diethyl ether (100 ml. each time) and the combined extracts were dried and evaporated to dryness. The residue was crystallised from a 1:1 v/v mixture of toluene and petroleum ether (b.p. 60—80°C.) at -50°C., and there was thus obtained 3,4-dichloro-*N*-methacryloylaniline, m.p. 120—122°C.

- 5 *m*-Chloroperbenzoic acid (3.4 g.) was added portionwise to a boiling solution of 3,4-dichloro-*N*-methacryloylaniline (2.2 g.) and 4-methyl-2,6-di-*t*-butylphenol (0.05 g.) in 1,1,1-trichloroethane (75 ml.) and the mixture was heated under reflux for 4 hours, cooled and washed successively (25 ml. portions each time) once with saturated aqueous sodium sulphite solution, twice with saturated aqueous sodium bicarbonate solution and once with saturated sodium chloride solution, dried over magnesium sulphate
10 and evaporated to dryness. The residue was purified by chromatography on a silica gel (Merck 7734) column using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant. The product was crystallised from petroleum ether (b.p. 60—80°C.) and there was thus obtained 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline, m.p. 90—92°C.

15 Example 4

The process described in Example 3 was repeated using the appropriate thiol and the appropriate *N*-(2,3-epoxy-2-methylpropionyl)aniline as starting materials, and there were thus obtained the compounds described in the following table:—



30

R ¹	R ²	R ⁷	m.p. (°C.)
Cl	Cl	thiazol-2-yl	105—107
Cl	Cl	pyrimidin-2-yl	103—105
CF ₃	NO ₂	2-chlorophenyl	98—100
CF ₃	NO ₂	3-chlorophenyl	132—133
CF ₃	NO ₂	4-chlorophenyl	101—103
CF ₃	NO ₂	4-fluorophenyl	112—113
CF ₃	NO ₂	4-cyanophenyl	108—111
CF ₃	NO ₂	4-nitrophenyl	139—141
CF ₃	NO ₂	4-methoxyphenyl	120—121
CF ₃	NO ₂	4-methylthiophenyl	111—112
CF ₃	NO ₂	n-pentyl	(oil)
CF ₃	NO ₂	2-hydroxyethyl	(oil)
CF ₃	NO ₂	allyl	80—81
CF ₃	NO ₂	2-methylallyl	78—79
CF ₃	NO ₂	cyclopentyl	87—88.5
CF ₃	NO ₂	pyrid-2-yl	155—157
CF ₃	NO ₂	pyrid-3-yl	149—150

65

	R ¹	R ²	R ⁷	m.p. (°C.)
5	CF ₃	NO ₂	pyrid-4-yl	193—195
	CF ₃	NO ₂	6-chloropyrid-2-yl	159—162
	CF ₃	NO ₂	thiazol-2-yl	131—132
10	CF ₃	NO ₂	4-methylthiazol-2-yl	160—162
	CF ₃	NO ₂	5-methyl-1,3,4-thiadiazol-2-yl	109—111
	CF ₃	CN	4-chlorophenyl	137—138
15	CF ₃	CN	4-fluorophenyl	116—117
	CF ₃	CN	4-methylthiophenyl	125—126
20	CF ₃	CN	pyrid-2-yl	137—139
	CF ₃	CN	pyrid-3-yl	135—136
	CF ₃	CN	5-chloropyrid-2-yl	113—115
25	CF ₃	CN	thien-2-yl	101—103
	CF ₃	CN	thiazol-2-yl	107—109
30	CF ₃	CN	4,5-dihydrothiazol-2-yl	110—111
	CF ₃	CN	1-methylimidazol-2-yl	112
	CF ₃	CN	benzthiazol-2-yl	178—180
35	CF ₃	CN	pyrimidin-2-yl	120—121

Similarly, by using the appropriate thiol and the appropriate *N*-(2,3-epoxy-2-methylbutyryl)aniline there were obtained:—

4-cyano-3-trifluoromethyl-*N*-[(2SR,3RS)-3-*p*-fluorophenylthio-2-hydroxy-2-methylbutyryl]aniline, m.p. 114—116°C. and 4-nitro-3-trifluoromethyl-*N*-[(2SR,3RS)-2-hydroxy-2-methyl-3-phenylthiobutyryl]aniline, m.p. 143—145°C.

The *N*-(2,3-epoxy-2-methylpropionyl or butyryl)anilines used as starting material were obtained by the epoxidation of the appropriate *N*-methacryloyl or *N*-methylcrotonoylaniline by a similar process to that described in the second part of Example 3. *N*-Methacryloyl-4-nitro-3-trifluoromethylaniline had m.p. 102—104°C. and the corresponding epoxy compound had m.p. 119—121°C.;

4-cyano-*N*-methacryloyl-3-trifluoromethylaniline had m.p. 137—139°C. and the corresponding epoxy-compound had m.p. 149—150°C.

N-(2-methylcrotonoyl)-4-nitro-3-trifluoromethylaniline had m.p. 65—67°C. and the corresponding epoxy compound had m.p. 99—102°C.;

4-cyano-*N*-(2-methylcrotonoyl)-3-trifluoromethylaniline had m.p. 127—128°C. and the corresponding epoxy compound had m.p. 100—103°C.

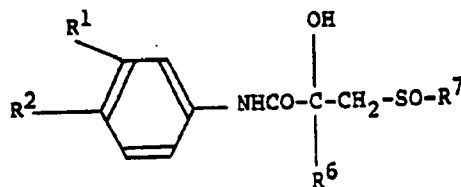
(The last two compounds are derived from *trans*-tiglic acid as opposed to *cis*-angelic acid).

Example 5

A solution of sodium metaperiodate (0.407 g.) in water (15 ml.) was added dropwise to a stirred solution of 4-cyano-3-trifluoromethyl-*N*-(3-ethylthio-2-hydroxy-2-trifluoromethylpropionyl)aniline (0.6 g.) in methanol (25 ml.) and the mixture was stirred at laboratory temperature for 48 hours and then filtered. The solid was washed with methanol (25 ml.) and the mixture was filtered, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (150 ml.) and the solution was washed successively with water (15 ml.), saturated aqueous sodium sulphite solution (25 ml.) and saturated aqueous sodium chloride solution (25 ml.), dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant, and the two

diastereoisomers of 4-cyano-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-trifluoromethylpropionyl)-aniline were obtained by evaporation of the appropriate fractions of the eluate. These had m.p. 141—143°C. (more polar isomer) and 160—162°C. (less polar isomer).

The process described above was repeated using the appropriate thiopropionylaniline as starting material, and there were thus obtained the compounds described in the following table:—

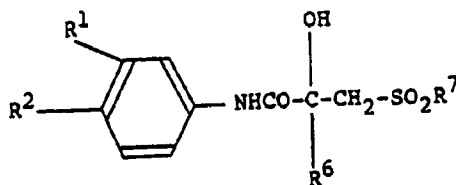


R ¹	R ²	R ⁶	R ⁷	Diastereoisomer	m.p. (°C.)
CF ₃	NO ₂	CH ₃	phenyl	more polar	126.5—127.5
CF ₃	CN	CH ₃	phenyl	more polar	164—165
CF ₃	CN	CH ₃	phenyl	mixed	175—176
CF ₃	CN	CH ₃	phenyl	mixed	110—112

Example 6

A solution of *m*-chloroperbenzoic acid (0.40 g.) in methylene chloride (80 ml.) was added to a stirred solution of 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline (0.38 g.) in methylene chloride (100 ml.) during 30 minutes and the reaction mixture was then stirred at laboratory temperature for 18 hours. Aqueous 10% w/v sodium sulphite gel solution (15 ml.) was added, the mixture was stirred and the organic layer was separated, washed successively twice with aqueous 10% w/v sodium carbonate solution (15 ml. each time) and once with saturated aqueous sodium chloride solution (15 ml.), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was dissolved in a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) and the solution was chromatographed on a silica gel column (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant. There was thus obtained 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylsulphonyl-2-trifluoromethylpropionyl)aniline, m.p. 175—176°C.

The process described above was repeated using the appropriate thiopropionylaniline as starting material and there were thus obtained the compounds described in the following table:—



	R ¹	R ²	R ⁶	R ⁷	m.p. (°C)
	CF ₃	NO ₂	CH ₃	phenyl	149—151
5	CF ₃	NO ₂	CH ₃	4-fluorophenyl	188—189
	CF ₃	NO ₂	CH ₃	pyrid-2-yl	148—150
10	CF ₃	NO ₂	CH ₃	ethyl	135—136
	CF ₃	NO ₂	CH ₃	n-propyl	118—119
	CF ₃	NO ₂	CH ₃	n-pentyl	104—105
15	CF ₃	CN	CH ₃	phenyl	172—173.5
	CF ₃	CN	CH ₃	4-fluorophenyl	189—191
20	CF ₃	CN	CH ₃	ethyl	116—118
	CF ₃	CN	CH ₃	n-propyl	117—119
	CF ₃	CN	CH ₃	ethyl	164—165
25	Cl	NO ₂	CH ₃	ethyl	145—146
	Cl	NO ₂	CH ₃	n-butyl	116—118
30	Cl	CN	CH ₃	ethyl	135—136
	CH ₃ O	CN	CH ₃	phenyl	172—173

Example 7

(-)-Camphanoyl chloride (4.33 g.) was added portionwise during 5 minutes to a solution of 4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline (5.8 g.) in pyridine (35 ml.) and the mixture was heated at 95°C. for 150 minutes and then evaporated to dryness. Toluene (50 ml.) was added and the mixture was again evaporated to dryness. The residue was dissolved in ethyl acetate (200 ml.) and the solution was washed with water (30 ml.) and then twice with saturated aqueous sodium chloride solution (20 ml. each time), dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (10 ml.) and the solution was flash chromatographed on silica gel (Merck 9385) using methylene chloride as eluant. There were thus obtained the two diastereoisomers of 4-cyano-3-trifluoromethyl-N-[2-(-)-camphanoyloxy-3-phenylthio-2-trifluoromethylpropionyl]aniline, the less polar isomer having m.p. 121—123°C. and the more polar isomer having m.p. 140—143°C.

A mixture of a solution of the less polar isomer (2.0 g.) in methanol (30 ml.) and aqueous 4% w/v sodium hydroxide solution (3.5 ml.) was stirred at laboratory temperature for 30 minutes and then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (160 ml.) and the solution was washed successively with water (25 ml.), saturated aqueous sodium chloride solution (25 ml.), and saturated aqueous sodium chloride solution (25 ml.), dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in methylene chloride (5 ml.) and flash-chromatographed on silica gel (Merck 9385) using methylene chloride as eluant. The product was crystallised from petroleum ether (b.p. 60—80°C.) and there was thus obtained (-)-4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline, m.p. 156—157°C., $[\alpha]_D^{23} = 43.8^\circ$ (C, 1% in methanol).

The process described in the preceding paragraph was repeated using the more polar isomer of the camphanoyl ester, and the product obtained was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. 60—80°C.). There was thus obtained (+)-4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline, m.p. 159—160°C., $[\alpha]_D^{23} = +45.5^\circ$ (C, 1% in methanol).

Example 8

The process described in Example 7 was repeated using 4-cyano-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline as the compound to be resolved. There were thus obtained the (-)-isomer, m.p. 94—96°C., $[\alpha]_D^{24} = -3.06^\circ$ (C, 1% in methanol) and the (+)-isomer, m.p. 95—97°C., $[\alpha]_D^{24} = +2.42^\circ$ (C, 1% in methanol).

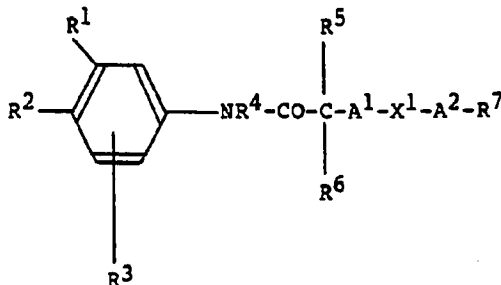
Example 9

n-Butyl-lithium (4.7 ml. of a 1.6 molar solution in hexane) was added during 2 minutes to a stirred solution of methylthiobenzene (0.82 ml.) and 1,4-diazabicyclo[2,2,2]octane (0.78 g.) in tetrahydrofuran (20 ml.) which was maintained at $-2^{\circ}\text{C}.$ under an atmosphere of argon. The mixture was allowed to warm up to $+2^{\circ}\text{C}.$, stirred at that temperature for 2 hours, cooled to $-65^{\circ}\text{C}.$ and a solution of *N*-(3,4-dichlorophenyl)pyruvamide (0.81 g.) in tetrahydrofuran (5 ml) was added during 5 minutes. The mixture was stirred and allowed to warm up to $-30^{\circ}\text{C}.$ during 90 minutes, aqueous 2N-hydrochloric acid (25 ml.) was added, the tetrahydrofuran was removed by evaporation under reduced pressure and the residue was extracted three times with diethyl ether (40 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution, dried and evaporated to dryness and the residue was purified by flash chromatography on a silica gel column (Merck 9385) using a 5:2 v/v mixture of petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and ethyl acetate as eluant. The product was crystallised from petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and there was thus obtained 3,4-dichloro-*N*-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline, m.p. $85-86^{\circ}\text{C}.$

The process described above was repeated using 4-bromo-2-methylsulphonylthiophen as starting material in place of methylthiobenzene. There was thus obtained *N*-[3-(4-bromothiophen-2-ylsulphonyl)-2-hydroxy-2-methylpropionyl]-3,4-dichloroaniline, m.p. $170-171^{\circ}\text{C}.$

'Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An acylanilide of the formula:—



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or halogen;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

wherein R^5 is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^4 to form an oxycarbonyl group such that together with the $—N—CO—C—$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula $—A^3—R^8$ or $—A^4—X^2—A^5—R^9$;

wherein A^1 and A^4 , which may be the same or different, each is alkylene of up to 6 carbon atoms;

wherein A^2 , A^3 and A^5 , which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X^1 and X^2 , which may be the same or different, each is sulphur, sulphinyl ($—SO—$) or sulphonyl ($—SO_2—$);

wherein R^7 and R^9 , which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R^7 or R^9 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^7 or R^9 is naphthyl; or R^7 or R^9 is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R^8 is phenyl, naphthyl or heterocyclic as defined above for R^7 or R^9 .

2. An acylanilide as claimed in claim 1 wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent.

3. An acylanilide as claimed in claim 1 wherein R¹ is trifluoromethyl, R² is cyano or nitro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link and R⁷ is alkyl of up to 3 carbon atoms, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

4. The compound

3-chloro-4-cyano-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)-aniline;

3-chloro-4-cyano-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylsulphonyl-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

3-chloro-4-nitro-*N*-(2-hydroxy-3-phenylthio-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-allylthio-2-hydroxy-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-

ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylsulphonyl)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)-aniline;

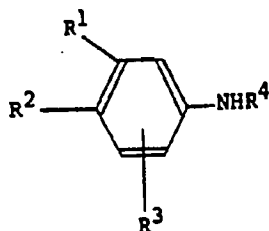
4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-methylthiopropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)-aniline.

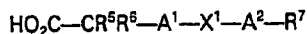
5. The compound 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline.

6. A process for the manufacture of an acylanilide, claimed in claim 1, which comprises

(a) the reaction of an amine of the formula:—

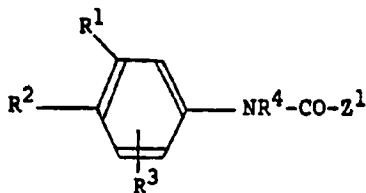


wherein R¹, R², R³ and R⁴ have the meanings stated in claim 1, with an acid of the formula:—

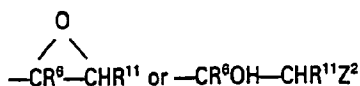


wherein R⁵, R⁶, R⁷, X¹, A¹ and A² have the meanings stated in claim 1, or with a reactive derivative of said acid; or

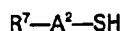
(b) for the manufacture of an acylanilide wherein R⁵ is hydroxy and X¹ is sulphur, the reaction of an epoxide of the formula:—



wherein R¹, R², R³ and R⁴ have the meanings stated above and wherein Z¹ has the formula

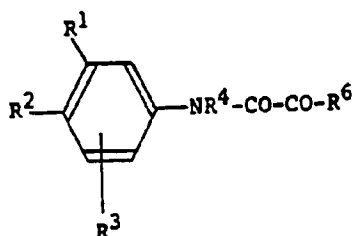


5 wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $-\text{CHR}^{11}-$ is $-\text{A}^1-$ as stated above, with a thiol of the formula:—

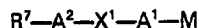


10 wherein R^7 and A^2 have the meanings stated above; or

(c) for the manufacture of an acylanilide wherein R^5 is hydroxy, the reaction of a compound of the formula:—

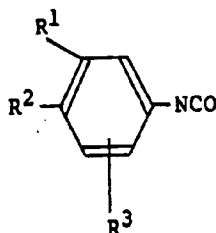


15
20
25 wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings stated above, with an organometallic compound of the formula:—

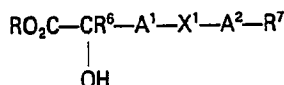


30 wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical; or

(d) for the manufacture of an acylanilide of the invention wherein R^4 and R^5 are joined together to form a carbonyloxy group, the reaction of an isocyanate of the formula:—



35
40
45 wherein R^1 , R^2 and R^3 have the meanings stated above, with an ester of the formula:—



50 wherein R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms: whereafter

(i) an acylanilide wherein R^5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy; or

(ii) an acylanilide wherein R^5 is hydroxy and R^4 is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in paragraph (d) above; or

55 (iii) an acylanilide wherein R^4 is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R^4 is hydrogen; or

(iv) an acylanilide wherein R^5 is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R^5 is hydroxy; or

(v) an oxazolidinedione wherein R^4 and R^5 are joined together to form a carbonyloxy group may be prepared by the reaction of the corresponding acylanilide wherein R^4 is hydrogen and R^5 is hydroxy with phosgene (COCl_2); or

60 (vi) an acylanilide wherein X^1 or X^2 is sulphinyl or sulphonyl or wherein one or more of R^1 , R^2 and a substituent in the phenyl or heterocyclic group R^7 , R^8 or R^9 is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein X^1 or X^2 is sulphur or wherein one or more of R^1 , R^2 and

a substituent in the phenyl or heterocyclic group R^7 , R^8 or R^9 is alkylthio, perfluoroalkylthio or phenylthio, respectively; or (vi) a racemic acylanilide wherein R^5 is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R^5 with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

5 7. A pharmaceutical or veterinary composition which comprises an acylanilide, claimed in claim 1, in association with a pharmaceutically-acceptable diluent or carrier.

8. A composition as claimed in claim 7 which is in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion; or in the form of a sterile solution or suspension suitable for parenteral administration; or in the form of an ointment or lotion for topical administration, or
10 in the form of a suppository for anal or vaginal administration.

9. A composition as claimed in claim 7 which additionally contains one or more drugs selected from anti-oestrogens, aromatase inhibitors, progestins, inhibitors of gonadotrophin secretion, LH—RH— analogues, cytotoxic agents, antibiotics and anti-inflammatory agents.

10. The use of a compound, claimed in any of claims 1 to 5 for the manufacture of a medicament for
15 producing an antiandrogenic effect in a warm blooded animal.

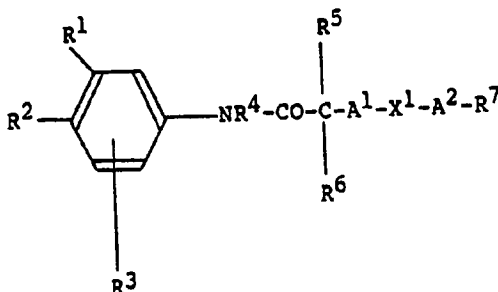
Claims for the Contracting State: AT

1. A process for the manufacture of an acylanilide of the formula:—

20

25

30



35 wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

40 wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or halogen;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

45 wherein R^5 is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^4 to form an oxycarbonyl group such that together with the $-N-CO-C-$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula $-A^3-R^8$ or $-A^4-X^2-A^5-R^9$;

wherein A^1 and A^4 , which may be the same or different, each is alkylene of up to 6 carbon atoms;

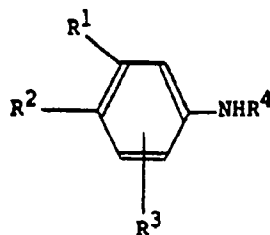
50 wherein A^2 , A^3 and A^5 , which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X^1 and X^2 , which may be the same or different, each is sulphur, sulphinyl ($-SO-$) or sulphonyl ($-SO_2-$);

55 wherein R^7 and R^9 , which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R^7 or R^9 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^7 or R^9 is naphthyl; or R^7 or R^9 is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R^8 is phenyl, naphthyl or heterocyclic as defined above for R^7 or R^9 , characterised by:—
65

(a) the reaction of an amine of the formula:—

5



10

wherein R¹, R², R³ and R⁴ have the meanings stated above, with an acid of the formula:—

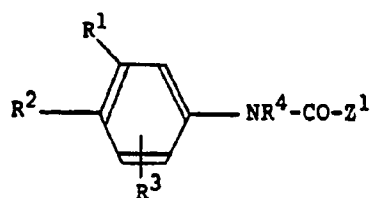
15



wherein R⁵, R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, or with a reactive derivative of said acid; or

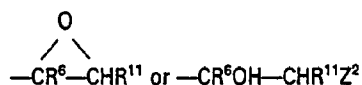
(b) for the manufacture of an acylanilide wherein R⁵ is hydroxy and X¹ is sulphur, the reaction of an epoxide of the formula:—

25



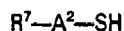
wherein R¹, R², R³ and R⁴ have the meanings stated above and wherein Z¹ has the formula

35



wherein R⁶ has the meaning stated above, wherein Z² is a displaceable group and wherein R¹¹ is such that —CHR¹¹— is —A¹— as stated above, with a thiol of the formula:—

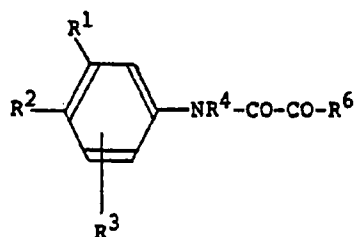
40



wherein R⁷ and A² have the meanings stated above; or

(c) for the manufacture of an acylanilide wherein R⁵ is hydroxy, the reaction of a compound of the formula:—

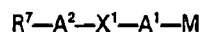
45



50

wherein R¹, R², R³, R⁴ and R⁶ have the meanings stated above, with an organometallic compound of the formula:—

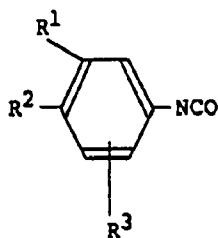
55



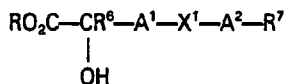
wherein A¹, A², R⁷ and X¹ have the meanings stated above and M is a metal radical; or

(d) for the manufacture of an acylanilide of the invention wherein R⁴ and R⁵ are joined together to form a carbonyloxy group, the reaction of an isocyanate of the formula:—

65



wherein R¹, R² and R³ have the meanings stated above, with an ester of the formula:—



wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms: whereafter

(i) an acylanilide wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy; or

(ii) an acylanilide wherein R⁵ is hydroxy and R⁴ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in paragraph (d) above; or

(iii) an acylanilide wherein R⁴ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R⁴ is hydrogen; or

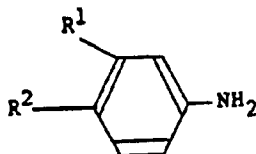
(iv) an acylanilide wherein R⁵ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R⁵ is hydroxy; or

(v) an oxazolidinedione wherein R⁴ and R⁵ are joined together to form a carbonyloxy group may be prepared by the reaction of the corresponding acylanilide wherein R⁴ is hydrogen and R⁵ is hydroxy with phosgene (COCl₂); or

(vi) an acylanilide wherein X¹ or X² is sulphonyl or sulphinyl, or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, or is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, may be prepared by the oxidation of the corresponding acylanilide wherein X¹ or X² is sulphur, or wherein more of R¹, R², and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylthio, perfluoroalkylthio or phenylthio, respectively; or (vi) a racemic acylanilide wherein R⁵ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

2. A process for the manufacture of an acylanilide of the formula stated in claim 1 wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphinyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent, characterised by:—

(a) the reaction of an amine of the formula:—

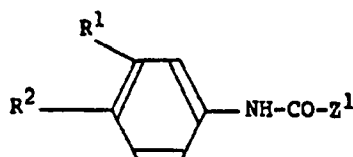


wherein R¹ and R² have the meanings stated above, with an acid of the formula:—

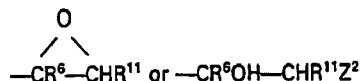


wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above and R⁵ is hydroxy or acyloxy as stated in claim 1, or with a reactive derivative of said acid; or

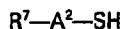
(b) for the manufacture of an acylanilide wherein X¹ is sulphur, the reaction of an epoxide of the formula:—



wherein R^1 and R^2 have the meanings stated above and wherein Z^1 has the formula

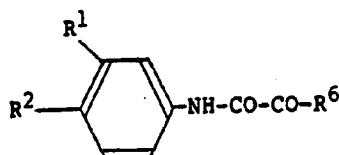


wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $-\text{CHR}^{11}-$ is $-\text{A}^1-$ as stated above, with a thiol of the formula:—

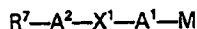


wherein R^7 and A^2 have the meanings stated above; or

(c) the reaction of a compound of the formula:—

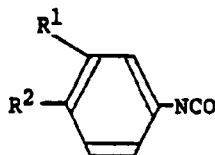


wherein R^1 , R^2 and R^6 have the meanings stated above, with an organometallic compound of the formula:—

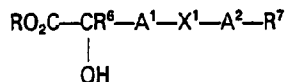


wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical; or

(d) the reaction of an isocyanate of the formula:—



wherein R^1 and R^2 have the meanings stated above, with an ester of the formula:—



wherein R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, followed by hydrolysis of the oxazolidinedione thus obtained; whereafter

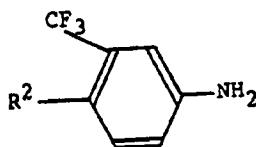
(i) an acylanilide wherein R^5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy; or

(ii) an acylanilide wherein X^1 is sulphinyl or sulphonyl may be prepared by the oxidation of the corresponding acylanilide wherein X^1 is sulphur; or

(iii) a racemic acylanilide may be separated into its optical isomers by forming an ester of the hydroxy group R^5 with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

3. A process for the manufacture of an acylanilide of the formula stated in claim 1 wherein R^1 is trifluoromethyl, R^2 is cyano or nitro, R^3 and R^4 are both hydrogen, R^5 is hydroxy, R^6 is methyl, A^1 is methylene, X^1 is sulphur, sulphinyl or sulphonyl, A^2 is a direct link and R^7 is alkyl of up to 3 carbon atoms, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl, characterised by:—

(a) the reaction of an amine of the formula:—

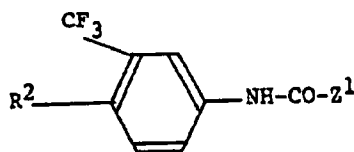


wherein R² has the meaning stated above, with an acid of the formula:—

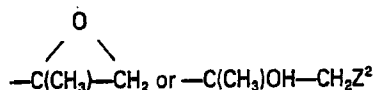


wherein R⁷ and X¹ have the meanings stated above and R⁵ is hydroxy or acyloxy as stated in claim 1, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein X¹ is sulphur, the reaction of an epoxide of the formula:—



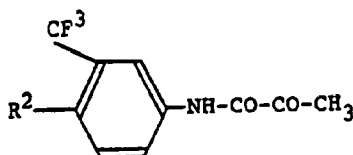
wherein R² has the meaning stated above and wherein Z¹ has the formula



wherein Z² is a displaceable group, with a thiol of the formula:—

wherein R⁷ has the meaning stated above; or

(c) reaction of a compound of the formula:—



wherein R² has the meaning stated above, with an organometallic compound of the formula:—



wherein R⁷ and X¹ have the meanings stated above and M is a metal radical; whereafter

(i) an acylanilide wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy; or

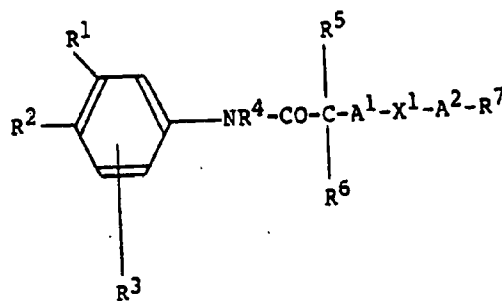
(ii) an acylanilide wherein X¹ is sulphonyl or sulphonyl may be prepared by the oxidation of the corresponding acylanilide wherein X¹ is sulphur; or

(iii) a racemic acylanilide may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

4. A process as claimed in claim 1, 2 or 3 wherein in the starting materials R¹ is trifluoromethyl, R² is cyano, R³ and R⁴ are both hydrogen, R⁵ is hydroxy or acyloxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur or sulphonyl, A² is a direct link and R⁷ is *p*-fluorophenyl, whereafter if R⁵ is acyloxy the compound is hydrolysed to the corresponding compound wherein R⁵ is hydroxy, and if X¹ is sulphur the compound is oxidised to the corresponding compound wherein X¹ is sulphonyl.

Patentsprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Acylanilid der Formel



worin R¹ für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo, Jodo oder Wasserstoff oder Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R² für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo oder Jodo oder Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R³ für Wasserstoff oder Halogen steht;

worin R⁴ für Wasserstoff oder Alkyl mit bis zu 4 Kohlenstoffatomen steht oder mit R⁵ verbunden ist, wie es nachstehend angegeben ist;

worin R⁵ für Hydroxy oder Alkoxy oder Acyloxy mit jeweils bis zu 15 Kohlenstoffatomen steht oder mit R⁴ unter Bildung einer Oxycarbonylgruppe verbunden ist, so daß es zusammen mit dem —N—CO—C— Teil des Moleküls eine Oxazolidindiongruppe bildet;

worin R⁶ für Alkyl oder Halogenoalkyl mit bis zu 4 Kohlenstoffatomen steht oder die Formel —A³—R⁸ oder —A⁴—X²—A⁵—R⁹ aufweist;

worin A¹ und A⁴, welche gleich oder verschieden sein können, jeweils für Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin A², A³ und A⁵, welche gleich oder verschieden sein können, jeweils für eine direkte Bindung oder Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin X¹ und X², welche gleich oder verschieden sein können, jeweils für Schwefel, Sulfinyl (—SO—) oder Sulfonyl (—SO₂—) stehen;

worin R⁷ und R⁹, welche gleich oder verschieden sein können, jeweils für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen stehen oder R⁷ oder R⁹ für Phenyl steht, das einen, zwei oder drei Substituenten trägt, die ausgewählt sind aus Wasserstoff, Halogen, Nitro, Carboxy, Carbamoyl und Cyano und Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl, Perfluoroalkylsulfonyl, Alkoxy-carbonyl und N-Alkyl-carbamoyl mit jeweils bis zu 4 Kohlenstoffatomen und Phenyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl, oder R⁷ oder R⁹ für Naphthyl steht oder R⁷ oder R⁹ für einen 5- oder 6-gliedrigen, gesättigten oder ungesättigten Heterozyklus steht, der ein, zwei oder drei Heteroatome enthält, die ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, welcher Heterozyklus ein einzelner Ring sein kann oder an einen Benzoring kondensiert sein kann und welcher Heterozyklus unsubstituiert ist oder einen oder zwei Halogen-, Cyano- oder Aminosubstituenten oder Alkyl-, Alkoxy-, Alkylthio-, Alkylsulfinyl- oder Alkylsulfonylsubstituenten mit jeweils bis zu 4 Kohlenstoffatomen oder Oxy- oder Hydroxysubstituenten trägt, oder welcher, sofern er ausreichend gesättigt ist, einen oder zwei Oxosubstituenten tragen kann; und

worin R⁸ für Phenyl, Naphthyl oder einen Heterozyklus, wie er oben für R⁷ oder R⁹ definiert ist, steht.

2. Acylanilid nach Anspruch 1, worin R¹ für Cyano, Nitro, Trifluoromethyl, Chloro, Methyl oder Methoxy steht, R² für Cyano, Nitro, Trifluoromethyl oder Chloro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl oder Trifluoromethyl steht, A¹ für Methylen, Ethylen oder Ethylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung oder Methylen steht und R⁷ für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen oder Phenyl, das unsubstituiert ist oder einen Fluoro-, Chloro-, Cyano-, Nitro-, Methoxy- oder Methylthiosubstituenten trägt, oder Thienyl, Imidazolyl, Thiazolyl, Benzothiazolyl, Thiadiazolyl, Pyridyl oder Pyrimidinyl, das unsubstituiert ist oder einen Chloro-, Bromo- oder Methylsubstituenten trägt, steht.

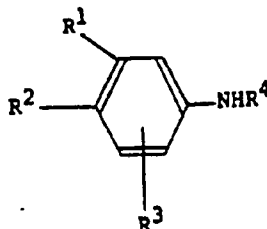
3. Acylanilid nach Anspruch 1, worin R¹ für Trifluoromethyl steht, R² für Cyano oder Nitro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl steht, A¹ für Methylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung steht und R⁷ für Alkyl mit bis zu 3 Kohlenstoffatomen oder Allyl, Phenyl, p-Fluorophenyl, Thiazol-2-yl, 4-Methylthiazol-2-yl, 5-Methyl-1,3,4-thiadiazol-2-yl oder 2-Pyridyl steht.

4. Die Verbindungen

- 3-Chloro-4-cyano-N-(2-ethylthio-2-hydroxy-2-methylpropionyl)anilin,
 3-Chloro-4-cyano-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-phenylsulfonylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(2-hydroxy-3-phenylsulfonyl-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 3-Chloro-4-nitro-N-(2-hydroxy-3-phenylthio-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-(3-allylthio-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylsulfonyl)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-(3-p-fluorophenylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl]anilin,
 4-Cyano-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl]anilin,
 4-Cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-methylthiopropionyl)anilin und
 4-Cyano-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)anilin.

5. Die Verbindung 4-Cyano-3-trifluoromethyl-N-(3-p-fluorophenylsulfonyl-2-hydroxy-2-methylpropionyl)anilin.

6. Verfahren zur Herstellung eines Acylanilids nach Anspruch 1, bei welchem
 (a) ein Amin der Formel

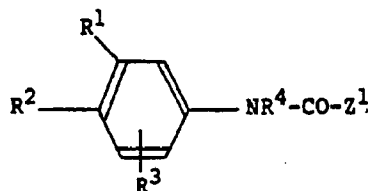


worin R¹, R², R³ und R⁴ die in Anspruch 1 angegebenen Bedeutungen besitzen, mit einer Säure der Formel

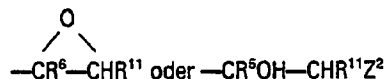


worin R⁵, R⁶, R⁷, X¹, A¹ und A² die in Anspruch 1 angegebenen Bedeutungen besitzen, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

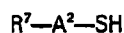
(b) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht und X¹ für Schwefel steht, ein Epoxid der Formel



worin R¹, R², R³ und R⁴ die oben angegebenen Bedeutungen besitzen und worin Z¹ die Formel

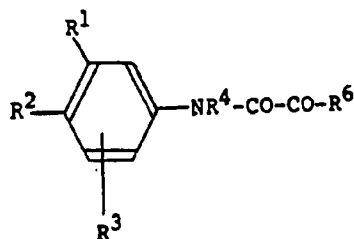


aufweist, worin R⁶ die oben angegebene Bedeutung besitzt, worin Z² für eine ersetzbare Gruppe steht und worin R¹¹ so ausgebildet ist, daß $-\text{CHR}^{11}-$ für $-\text{A}^1-$, wie es oben angegeben ist, steht, mit einem Thiol der Formel



worin R⁷ und A² die oben angegebenen Bedeutungen besitzen, umgesetzt wird, oder

(c) zur Herstellung eines Acylanilids, worin R^5 für Hydroxy steht, eine Verbindung der Formel

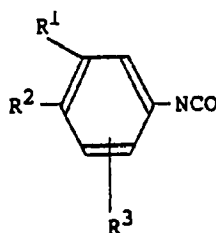


worin R^1 , R^2 , R^3 , R^4 und R^6 die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel

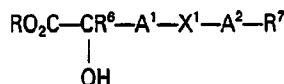


worin A^1 , A^2 , R^7 und X^1 die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird oder

(d) zur Herstellung eines Acylanilids, worin R^4 und R^5 unter Bildung einer Carbonyloxygruppe miteinander verbunden sind, ein Isocyanat der Formel



worin R^1 , R^2 und R^3 die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel



worin R^6 , R^7 , X^1 , A^1 und A^2 die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird, worauf

(i) ein Acylanilid, worin R^5 für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R^5 für Acyloxy steht, hergestellt werden kann oder

(ii) ein Acylanilid, worin R^5 für Hydroxy steht und R^4 für Wasserstoff steht, durch Hydrolyse des entsprechenden Oxazolidindions, das wie oben im Absatz (d) angegeben herstellbar ist, hergestellt werden kann oder

(iii) ein Acylanilid, worin R^4 für Alkyl steht, durch Alkylierung des entsprechenden Acylanilids, worin R^4 für Wasserstoff steht, hergestellt werden kann oder

(iv) ein Acylanilid, worin R^5 für Acyloxy steht, durch Acylierung des entsprechenden Acylanilids, worin R^5 für Hydroxy steht, hergestellt werden kann oder

(v) ein Oxazolidindion, worin R^4 und R^5 miteinander unter Bildung einer Carbonyloxygruppe verbunden sind, durch Umsetzung des entsprechenden Acylanilids, worin R^4 für Wasserstoff steht und R^5 für Hydroxy steht, mit Phosgen ($COCl_2$) hergestellt werden kann oder

(vi) ein Acylanilid, worin X^1 oder X^2 für Sulfinyl oder Sulfonyl steht oder worin einer oder mehrere der Substituenten R^1 und R^2 und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R^7 , R^8 oder R^9 für Alkylsulfinyl, Perfluoroalkylsulfinyl oder Phenylsulfinyl oder für Alkylsulfonyl, Perfluoroalkylsulfonyl oder Phenylsulfonyl stehen, durch Oxidation des entsprechenden Acylanilids, worin X^1 oder X^2 für Schwefel steht oder worin einer oder mehrere der Substituenten R^1 und R^2 und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R^7 , R^8 oder R^9 für Alkylthio, Perfluoroalkylthio bzw. Phenylthio stehen, hergestellt werden kann oder

(vii) ein racemisches Acylanilid, worin R^5 für Hydroxy steht, in optische Isomere getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R^5 mit einer optisch aktiven Säure, Trennen der so erhaltenen diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

7. Pharmazeutische oder veterinäre Zusammensetzung, welche ein Acylanilid nach Anspruch 1 gemeinsam mit einem pharmazeutisch zulässigen Verdünnungs- oder Trägermittel enthält.

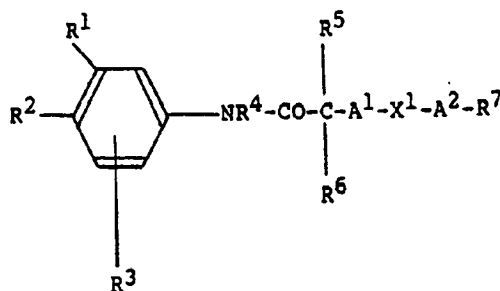
8. Zusammensetzung nach Anspruch 7, welche eine für orale Dosierung geeignete Form, wie z.B. einer Tablette, Kapsel, wäßrigen oder öligen Lösung oder Suspension oder Emulsion, oder die Form einer für parenterale Verabreichung geeigneten sterilen Lösung oder Suspension oder die Form einer für topische Verabreichung geeigneten Salbe oder Lotion oder die Form eines für anale oder vaginale Verabreichung geeigneten Suppositoriums aufweist.

9. Zusammensetzung nach Anspruch 7, welche zusätzlich einem oder mehrere Wirkstoffe enthält, die ausgewählt sind aus Antiöstrogenen, Aromataseinhibitoren, Progestinen, Inhibitoren der Gonadotrophinsekretion, LH—RH-Analogen, cytotoxischen Mitteln, Antibiotika und antiinflammatorischen Mitteln.

10. Die Verwendung einer Verbindung nach einem der Ansprüche 1 bis 5 für die Herstellung eines Medikaments zur Erzeugung eines antiandrogenen Effekts bei Warmblütern.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Acylanilids der Formel



worin R¹ für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo, Jodo oder Wasserstoff oder Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R² für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo oder Jodo oder Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R³ für Wasserstoff oder Halogen steht;

worin R⁴ für Wasserstoff oder Alkyl mit bis zu 4 Kohlenstoffatomen steht oder mit R⁶ verbunden ist, wie es nachstehend angegeben ist;

worin R⁵ für Hydroxy oder Alkoxy oder Acyloxy mit jeweils bis zu 15 Kohlenstoffatomen steht oder mit R⁴ unter Bildung einer Oxycarbonylgruppe verbunden ist, so daß es zusammen mit dem —N—CO—C— Teil des Moleküls eine Oxazolidindiongruppe bildet;

worin R⁶ für Alkyl oder Halogenoalkyl mit bis zu 4 Kohlenstoffatomen steht oder die Formel —A³—R⁸ oder —A⁴—X²—A⁵—R⁹ aufweist;

worin A¹ und A⁴, welche gleich oder verschieden sein können, jeweils für Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin A², A³ und A⁵, welche gleich oder verschieden sein können, jeweils für eine direkte Bindung oder Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

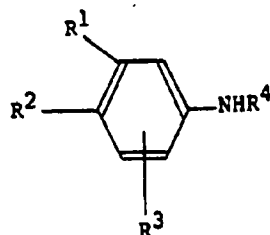
worin X¹ und X², welche gleich oder verschieden sein können, jeweils für Schwefel, Sulfinyl (—SO—) oder Sulfonyl (—SO₂—) stehen;

worin R⁷ und R⁹, welche gleich oder verschieden sein können, jeweils für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen stehen oder R⁷ oder R⁹ für Phenyl steht, das einen, zwei oder drei Substituenten trägt, die ausgewählt sind aus Wasserstoff, Halogen, Nitro, Carboxy, Carbamoyl und Cyano und Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl, Perfluoroalkylsulfonyl, Alkoxy-carbonyl und N-Alkylcarbamoyl mit jeweils bis zu 4 Kohlenstoffatomen und Phenyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl, oder R⁷ oder R⁹ für Naphthyl steht oder R⁷ oder R⁹ für einen 5- oder 6-gliedrigen, gesättigten oder ungesättigten Heterozyklus steht, der ein, zwei oder drei Heteroatome enthält, die ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, welcher Heterozyklus ein einzelner Ring sein kann oder an einen Benzoring kondensiert sein kann und welcher Heterozyklus unsubstituiert ist oder einen oder zwei Halogen-, Cyano- oder Aminosubstituenten oder Alkyl-, Alkoxy-, Alkylthio-, Alkylsulfinyl- oder Alkylsulfonylsubstituenten mit jeweils bis zu 4 Kohlenstoffatomen oder Oxy- oder Hydroxysubstituenten trägt, oder welcher, sofern er ausreichend gesättigt ist, einen oder zwei Oxosubstituenten tragen kann; und

worin R⁸ für Phenyl, Naphthyl oder einen Heterozyklus, wie er oben für R⁷ oder R⁹ definiert ist, steht, dadurch gekennzeichnet, daß

(a) ein Amin der Formel

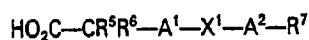
5



10

worin R¹, R², R³ und R⁴ die in oben angegebenen Bedeutungen besitzen, mit einer Säure der Formel

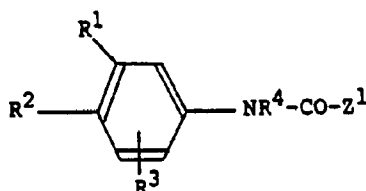
15



worin R⁵, R⁶, R⁷, X¹, A¹ und A² die in oben angegebenen Bedeutungen besitzen, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

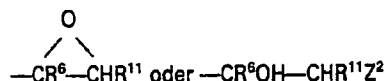
(b) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht und X¹ für Schwefel steht, ein Epoxid der Formel

20



25

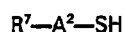
30 worin R¹, R², R³ und R⁴ die oben angegebenen Bedeutungen besitzen und worin Z¹ die Formel



35

aufweist, worin R⁶ die oben angegebene Bedeutung besitzt, worin Z² für eine ersetzbare Gruppe steht und worin R¹¹ so ausgebildet ist, daß -CHR¹¹- für -A¹-, wie es oben angegeben ist, steht, mit einem Thiol der Formel

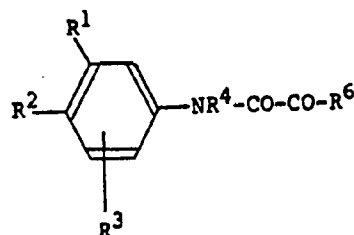
40



worin R⁷ und A² die oben angegebenen Bedeutungen besitzen, umgesetzt wird oder

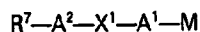
(c) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht, eine Verbindung der Formel

45



50

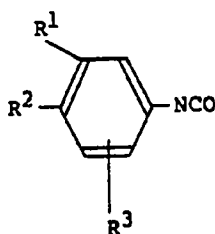
55 worin R¹, R², R³, R⁴ und R⁶ die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel



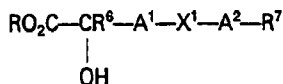
60 worin A¹, A², R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird oder

(d) zur Herstellung eines Acylanilids, worin R⁴ und R⁵ unter Bildung einer Carbonyloxygruppe miteinander verbunden sind, ein Isocyanat der Formel

65



worin R¹, R² und R³ die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel



worin R⁶, R⁷, X¹, A¹ und A² die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird, worauf

(i) ein Acylanilid, worin R⁵ für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R⁵ für Acyloxy steht, hergestellt werden kann oder

(ii) ein Acylanilid, worin R⁵ für Hydroxy steht und R⁴ für Wasserstoff steht, durch Hydrolyse des entsprechenden Oxazolidindions, das wie oben im Absatz (d) angegeben herstellbar ist, hergestellt werden kann oder

(iii) ein Acylanilid, worin R⁴ für Alkyl steht, durch Alkylierung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht, hergestellt werden kann oder

(iv) ein Acylanilid, worin R⁵ für Acyloxy steht, durch Acylierung des entsprechenden Acylanilids, worin R⁵ für Hydroxy steht, hergestellt werden kann oder

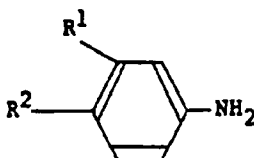
(v) ein Oxazolidindion, worin R⁴ und R⁵ miteinander unter Bildung einer Carbonyloxygruppe verbunden sind, durch Umsetzung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht und R⁵ für Hydroxy steht, mit Phosgen (COCl₂) hergestellt werden kann oder

(vi) ein Acylanilid, worin X¹ oder X² für Sulfinyl oder Sulfonyl steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylsulfinyl, Perfluoroalkylsulfinyl oder Phenylsulfinyl oder für Alkylsulfonyl, Perfluoroalkylsulfonyl oder Phenylsulfonyl stehen, durch Oxidation des entsprechenden Acylanilids, worin X¹ oder X² für Schwefel steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylthio, Perfluoroalkylthio bzw. Phenylthio stehen, hergestellt werden kann oder

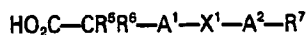
(vii) ein racemisches Acylanilid, worin R⁵ für Hydroxy steht, in optische Isomere getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R⁵ mit einer optisch aktiven Säure, Trennen der so erhaltenen diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

2. Verfahren zur Herstellung eines Acylanilids der Formel von Anspruch 1, worin R¹ für Cyano, Nitro, Trifluoromethyl, Chloro, Methyl oder Methoxy steht, R² für Cyano, Nitro, Trifluoromethyl oder Chloro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl oder Trifluoromethyl steht, A¹ für Methylen, Ethylen oder Ethylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung oder Methylen steht und R⁷ für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen oder Phenyl, das unsubstituiert ist oder einen Fluoro-, Chloro-, Cyano-, Nitro-, Methoxy- oder Methylthiosubstituenten trägt, oder Thienyl, Imidazolyl, Thiazolyl, Benzthiazolyl, Thiadiazolyl, Pyridyl oder Pyrimidinyl, das unsubstituiert ist oder einen Chloro-, Bromo- oder Methylsubstituenten trägt, steht, dadurch gekennzeichnet, daß

(a) ein Amin der Formel



worin R¹ und R² die oben angegebenen Bedeutungen besitzen, mit einer Säure der Formel

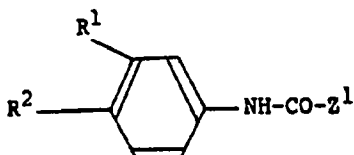


worin R⁶, R⁷, X¹, A¹ und A² die oben angegebenen Bedeutungen besitzen und R⁵ für Hydroxy oder Acyloxy,

wie es in Anspruch 1 angegeben ist, steht, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

(b) zur Herstellung eines Acylanilids, worin X^1 für Schwefel steht, ein Epoxid der Formel

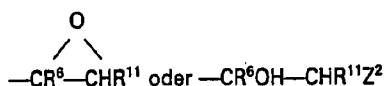
5



10

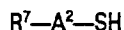
worin R^1 und R^2 die oben angegebenen Bedeutungen besitzen und worin Z^1 die Formel

15



20

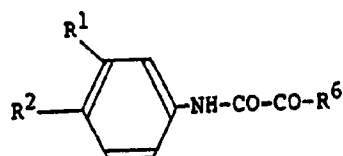
aufweist, worin R^6 die oben angegebene Bedeutung besitzt, worin Z^2 für eine ersetzbare Gruppe steht und worin R^{11} so ausgebildet ist, daß $-CHR^{11}-$ für $-A^1-$, wie es oben angegeben ist, steht, mit einem Thiol der Formel



25

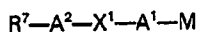
worin R^7 und A^2 die oben angegebenen Bedeutungen besitzen, umgesetzt wird, oder
(c) eine Verbindung der Formel

30



35

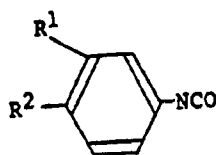
worin R^1 , R^2 und R^6 die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel



40

worin A^1 , A^2 , R^7 und X^1 die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird, oder
(d) ein Isocyanat der Formel

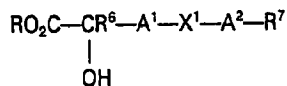
45



50

worin R^1 und R^2 die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel

55



60

worin R^6 , R^7 , X^1 , A^1 und A^2 die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird und hierauf das so erhaltene Oxazolidindion hydrolysiert wird, worauf

(i) ein Acylanilid, worin R^5 für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R^5 für Acyloxy steht, hergestellt werden kann oder

(ii) ein Acylanilid, worin X^1 für Sulfinyl oder Sulfonyl steht, durch Oxidation des entsprechenden Acylanilids, worin X^1 für Schwefel steht, hergestellt werden kann oder

65

(iii) ein racemisches Acylanilid in seine optischen Isomeren getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R^5 mit einer optisch aktiven Säure, Trennen der so erhaltenen

diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

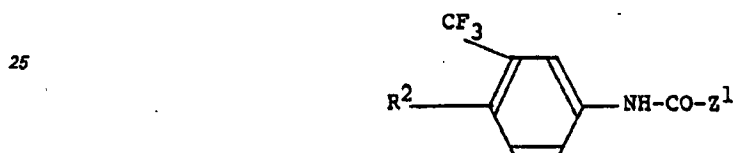
3. Verfahren zur Herstellung eines Acylanilids der Formel von Anspruch 1, worin R¹ für Trifluormethyl steht, R² für Cyano oder Nitro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl steht, A¹ für Methylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte
5 Bindung steht und R⁷ für Alkyl mit bis zu 3 Kohlenstoffatomen oder Allyl, Phenyl, p-Fluorophenyl, Thiazol-2-yl, 4-Methylthiazol-2-yl, 5-Methyl-1,3,4-thiadiazol-2-yl oder 2-Pyridyl steht, dadurch gekennzeichnet, daß
(a) ein Amin der Formel



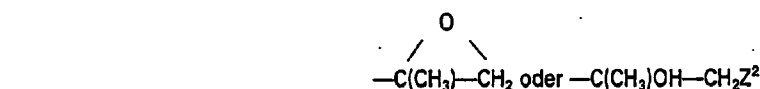
- 15 worin R² die oben angegebene Bedeutung besitzt, mit einer Säure der Formel



- worin R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und R⁵ für Hydroxy oder Acyloxy, wie es in
20 Anspruch 1 angegeben ist, steht, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder
(b) zur Herstellung eines Acylanilids, worin X¹ für Schwefel steht, ein Epoxid der Formel



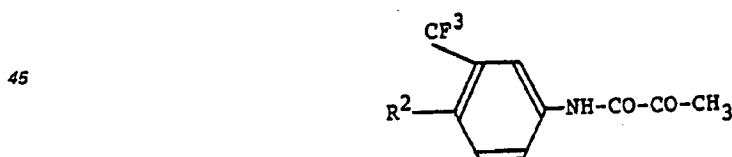
- 30 worin R² die oben angegebene Bedeutung besitzt und worin Z¹ die Formel



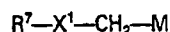
- aufweist, worin Z² für eine ersetzbare Gruppe steht, mit einem Thiol der Formel



- 40 worin R⁷ die oben angegebene Bedeutung besitzt, umgesetzt wird oder
(c) eine Verbindung der Formel



- 50 worin R² die oben angegebene Bedeutung besitzt, mit einer Organometallverbindung der Formel



- worin R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt
55 wird, worauf

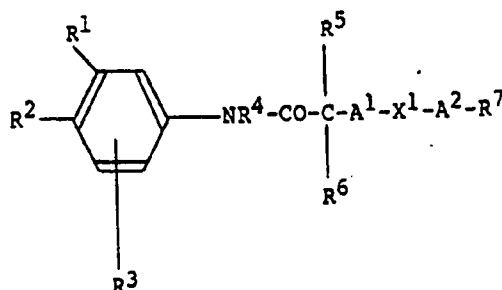
- (i) ein Acylanilid, worin R⁵ für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin
R⁵ für Acyloxy steht, hergestellt werden kann oder
(ii) ein Acylanilid, worin X¹ für Sulfinyl oder Sulfonyl steht, durch Oxidation des entsprechenden
Acylanilids, worin X¹ für Schwefel steht, hergestellt werden kann oder
60 (iii) ein racemisches Acylanilid in seine optischen Isomere getrennt werden kann durch Herstellen
eines Esters an der Hydroxygruppe R⁵ mit einer optisch aktiven Säure, Trennen der so erhaltenen
diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

4. Verfahren nach Anspruch 1, 2 oder 3, worin im Ausgangsmaterial R¹ für Trifluormethyl steht, R² für
Cyano steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy oder Acyloxy steht, R⁶ für Methyl steht,
65 A¹ für Methylen steht, X¹ für Schwefel oder Sulfonyl steht, A² für eine direkte Bindung steht und R⁷ für p-

Fluorophenyl steht, worauf, wenn R⁵ für Acyloxy steht, die Verbindung zur entsprechenden Verbindung, worin R⁵ für Hydroxy steht, hydrolysiert wird und, wenn X¹ für Schwefel steht, die Verbindung zur entsprechenden Verbindung, worin X¹ für Sulfonyl steht, oxidiert wird.

6 Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Acylanilide de formule:



dans laquelle

R¹ est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo, iodo ou un atome d'hydrogène, ou un groupe alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou

R² est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo ou iodo, ou un groupe alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R³ est l'hydrogène ou un halogène;

R⁴ est l'hydrogène ou un groupe alkyle ayant jusqu'à 4 atomes de carbone, ou est associé à R⁵ comme indiqué ci-dessous;

R⁵ est un groupe hydroxy or alkoxy ou un groupe acyloxy, chacun ayant jusqu'à 15 atomes de carbone, ou s'associe avec R⁴ pour former un groupe oxycarbonyle de manière à former avec la partie -N-CO-C- de la molécule un groupe oxazolidinedione;

R⁶ est un groupe alkyle ou halogénalkyle ayant jusqu'à 4 atomes de carbone ou répond à la formule -A³-R⁸ ou -A⁴-X²-A⁵-R⁹;

A¹ et A⁴, qui peuvent être identiques ou différents, représentent chacun un groupe alkylène ayant jusqu'à 6 atomes de carbone;

A², A³ et A⁵, qui peuvent être identiques ou différents, représentent chacun une liaison directe ou un groupe alkylène ayant jusqu'à 6 atomes de carbone;

X¹ et X², qui peuvent être identiques ou différents, représentent chacun le soufre, un groupe sulfinyle (-SO-) ou sulfonyle (-SO₂-);

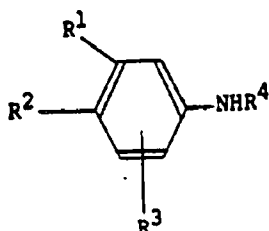
R⁷ et R⁹, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou bien R⁷ ou R⁹ est un groupe phényle qui porte un, deux ou trois substituants choisis entre l'hydrogène, un halogène, les groupes nitro, carboxy, carbamoyle et cyano, et des groupes alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle, perfluoralkylsulfonyle, alkoxycarbonyle et N-alkylcarbamoyle ayant chacun jusqu'à 4 atomes de carbone, et les groupes phényle, phénylthio, phénylsulfinyle et phénylsulfonyle; ou bien R⁷ ou R⁹ est un groupe naphthyle; ou bien R⁷ ou R⁹ est un noyau hétérocyclique saturé ou insaturé pentagonal ou hexagonal qui contient un, deux ou trois hétéro-atomes choisis entre des atomes d'oxygène, d'azote et de soufre, ce noyau hétérocyclique pouvant être un noyau simple ou un noyau condensé à un noyau benzénique, et ce noyau hétérocyclique n'étant pas substitué ou portant un ou deux substituants halogéno, cyano ou amino, ou alkyle, alkoxy, alkylthio, alkylsulfinyle ou alkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou des substituants oxy ou hydroxy, ou qui peut porter, s'il est suffisamment saturé, un ou deux substituants oxy; et R⁸ est un groupe phényle, naphthyle ou un noyau hétérocyclique tel que défini ci-dessus pour R⁷ ou R⁹.

2. Acylanilide suivant la revendication 1, dans lequel R¹ est un groupe cyano, nitro, trifluorométhyle, chloro, méthyle ou méthoxy, R² est un groupe cyano, nitro, trifluorométhyle ou chloro, R³ et R⁴ sont tous deux de l'hydrogène, R⁵ est un groupe hydroxy, R⁶ est un groupe méthyle ou trifluorométhyle, A¹ est un groupe méthylène, éthylène ou éthylidène, X¹ est le soufre, un groupe sulfinyle ou sulfonyle, A² est une liaison directe ou un groupe méthylène et R⁷ est un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle, chacun ayant jusqu'à 6 atomes de carbone, ou un groupe phényle qui n'est pas substitué ou qui porte un substituant fluoro, chloro, cyano, nitro, méthoxy ou méthylthio, ou un groupe thiénylène, imidazolyle,

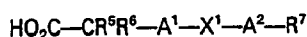
thiazolyle, benzothiazolyle, thiadiazolyle, pyridyle ou pyrimidinyle qui n'est pas substitué ou qui porte un substituant chloro, bromo ou méthyle.

3. Acylanilide suivant la revendication 1, dans lequel R¹ est un groupe trifluorométhyle, R² est un groupe cyano ou nitro, R³ et R⁴ sont tous deux de l'hydrogène, R⁵ est un groupe hydroxy, R⁶ est un groupe méthyle, A¹ est un groupe méthylène, X¹ est le soufre, un groupe sulfinyle ou sulfonyle, A² est une liaison directe et R⁷ est un groupe alkyle ayant jusqu'à 3 atomes de carbone, ou est un groupe allyle, phényle, *p*-fluorophényle, thiazole-2-yle, 4-méthylthiazole-2-yle, 5-méthyl-1,3,4-thiadiazole-2-yle ou 2-pyridyle.

4. La 3-chloro-4-cyano-*N*-(3-éthylthio-2-hydroxy-2-méthylpropionyl)-aniline;
 la 3-chloro-4-cyano-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-phénylsulfonylpropionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-3-phénylsulfonyl-2-méthylpropionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)aniline;
 la 3-chloro-4-nitro-*N*-(2-hydroxy-3-phénylthio-2-méthylpropionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(thiazole-2-ylthio)propionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-allylthio-2-hydroxy-2-méthylpropionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-*p*-fluorophénylthio-2-hydroxy-2-méthylpropionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylthio)propionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(5-méthyl-1,3,4-thiadiazole-2-ylthio)propionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(4-méthylthiazole-2-ylthio)propionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylsulfonyl)propionyl)aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-*p*-fluorophénylsulfonyl-2-hydroxy-2-méthylpropionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(thiazole-2-ylthio)propionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylthio)propionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-méthylthiopropionyl)aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(3-*p*-fluorophénylthio-2-hydroxy-2-méthylpropionyl)aniline.
 5. La 4-cyano-3-trifluorométhyl-*N*-(3-*p*-fluorophénylsulfonyl-2-hydroxy-2-méthylpropionyl)aniline.
 6. Procédé de production d'un acylanilide suivant la revendication 1, qui comprend
 (a) la réaction d'une amine de formule:

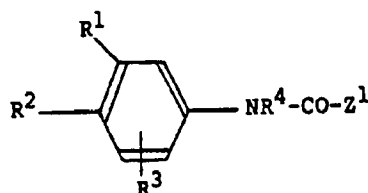


dans laquelle R¹, R², R³ et R⁴ ont les définitions données dans la revendication 1, avec un acide de formule:

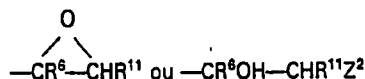


dans laquelle R⁵, R⁶, R⁷, X¹, A¹ et A² ont les définitions indiquées dans la revendication 1, ou avec un dérivé réactif de cet acide; ou bien

(b) pour la production d'un acylanilide dans lequel R⁵ est un groupe hydroxy et X¹ est le soufre, la réaction d'un époxyde de formule:

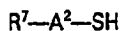


dans laquelle R¹, R², R³ et R⁴ ont les définitions indiquées ci-dessus et Z¹ répond à la formule



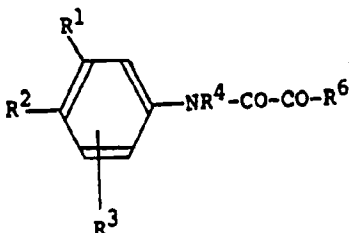
dans laquelle R⁶ a la définition indiquée ci-dessus, Z² est un groupe déplaçable et R¹¹ est choisi de manière

que $\text{—CHR}^{11}\text{—}$ représente $\text{—A}^1\text{—}$ tel que défini ci-dessus, avec un thiol de formule:

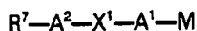


5 dans laquelle R^7 et A^2 ont les définitions données ci-dessus; ou

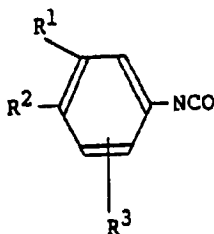
(c) pour la production d'un acylanilide dans lequel R^5 est un groupe hydroxy, la réaction d'un composé de formule:



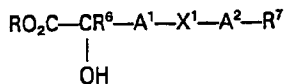
10 dans laquelle R^1 , R^2 , R^3 , R^4 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule;



20 dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un métal alcalin; ou bien
 25 (d) pour la production d'un acylanilide de l'invention dans lequel R^4 et R^5 forment conjointement un groupe carbonyloxy, la réaction d'un isocyanate de formule:



30 dans laquelle R^1 , R^2 et R^3 ont les définitions indiquées ci-dessus, avec un ester de formule:



40 dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus, et R est un groupe alkyle ayant jusqu'à 6 atomes de carbone; après quoi

45 (i) un acylanilide dans lequel R^5 est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R^5 est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel R^5 est un groupe hydroxy et R^4 est l'hydrogène peut être préparé par l'hydrolyse de l'oxazolidinedione correspondante, qui peut être préparée comme décrit dans le paragraphe
 50 (d) ci-dessus; ou bien

(iii) ou acylanilide dans lequel R^4 est un groupe alkyle peut être préparé par alkylation de l'acylanilide correspondant dans lequel R^4 est l'hydrogène; ou bien

(iv) un acylanilide dans lequel R^5 est un groupe acyloxy peut être préparé par acylation de l'acylanilide correspondant dans lequel R^5 est un groupe hydroxy; ou bien

55 (v) une oxazolidinedione dans laquelle R^4 et R^5 forment conjointement un groupe carbonyloxy peut être préparée par réaction de l'acylanilide correspondant dans lequel R^4 est l'hydrogène et R^5 est un groupe hydroxy, avec le phosgène (COCl_2); ou bien

(vi) un acylanilide dans lequel X^1 ou X^2 est un groupe sulfinyle ou sulfonyle ou dans lequel ou un
 60 plusieurs de R^1 , R^2 et un substituant du groupe phényle ou hétérocyclique R^7 , R^8 ou R^9 , sont un groupe alkylsulfinyle, perfluoralkylsulfinyle ou phénylsulfinyle, ou un groupe alkylsulfonyle, perfluoralkylsulfonyle ou phénylsulfonyle, peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X^1 ou X^2 est le soufre ou dans lequel un ou plusieurs de R^1 , R^2 et un substituant du groupe phényle ou hétérocyclique R^7 , R^8 ou R^9 sont, respectivement, un groupe alkylthio, perfluoralkylthio ou phénylthio; ou bien

65 (vi) un acylanilide racémique dans lequel R^5 est un groupe hydroxy peut être divisé en ses isomères

optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéréo-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

7. Composition pharmaceutique ou vétérinaire, qui comprend un acylanilide suivant la revendication 1 en association avec un diluant ou support pharmaceutiquement acceptable.

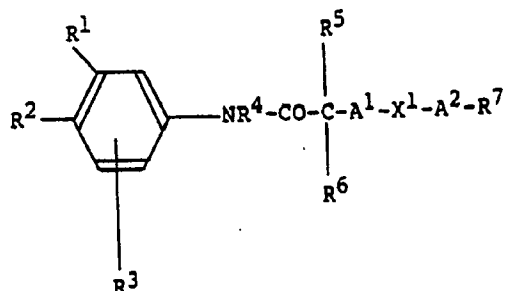
8. Composition suivant la revendication 7, qui est sous une forme qui convient pour l'administration orale, telle qu'un comprimé, une capsule, une solution ou suspension ou émulsion aqueuse ou huileuse; ou sous la forme d'une solution ou suspension stérile qui convient pour l'administration parentérale; ou sous la forme d'une pommade ou d'une lotion pour l'administration topique, ou sous la forme d'un suppositoire pour l'administration anale ou vaginale.

9. Composition suivant la revendication 7, qui contient en outre un ou plusieurs médicaments choisis entre des anti-oestrogènes, des inhibiteurs d'aromatase, des progestines, des inhibiteurs de sécrétion gonadotrope, des analogues de l'hormone libérant l'hormone lutéinisante, des agents cytotoxiques, des antibiotiques et des agents anti-inflammatoires.

10. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 5 pour la préparation d'un médicament destiné à produire un effet anti-androgénique chez un animal à sang chaud.

Revendications pour l'Etat contractant: AT

1. Procédé de production d'un acylanilide de formule:



dans laquelle

R¹ est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo, iodo ou un atome d'hydrogène, ou un groupe alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R² est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo ou iodo, ou un groupe alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R³ est l'hydrogène ou un halogène;

R⁴ est l'hydrogène ou un groupe alkyle ayant jusqu'à 4 atomes de carbone, ou est associé à R⁵ comme indiqué ci-dessous;

R⁵ est un groupe hydroxy or alkoxy ou un groupe acyloxy, chacun ayant jusqu'à 15 atomes de carbone, ou s'associe avec R⁴ pour former un groupe oxycarbonyle de manière à former avec la partie -N-CO-C- de la molécule un groupe oxazolidinedione;

R⁶ est un groupe alkyl ou halogénaalkyle ayant jusqu'à 4 atomes de carbone ou répond à la formule -A³-R⁸ ou -A⁴-X²-A⁵-R⁹;

A¹ et A⁴, qui peuvent être identiques ou différents, représentent chacun un groupe alkylène ayant jusqu'à 6 atomes de carbone;

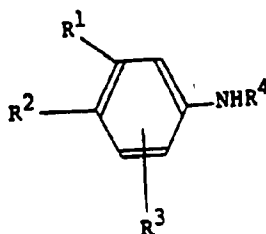
A², A³ et A⁵, qui peuvent être identiques ou différents, représentent chacun une liaison directe ou un groupe alkylène ayant jusqu'à 6 atomes de carbone;

X¹ et X², qui peuvent être identiques ou différents, représentent chacun le soufre, un groupe sulfinyle (-SO-) ou sulfonyle (-SO₂-);

R⁷ et R⁹, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou bien R⁷ ou R⁹ est un groupe phényle qui porte un, deux ou trois substituants choisis entre l'hydrogène, un halogène, les groupes nitro, carboxy, carbamoyle et cyano, et des groupes alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle, perfluoralkylsulfonyle, alkoxy-carbonyle et N-alkylcarbamoyle ayant chacun jusqu'à 4 atomes de carbone, et les groupes phényle, phénylthio, phénylsulfinyle et phénylsulfonyle; ou bien R⁷ ou R⁹ est un groupe naphtyle; ou bien R⁷ ou R⁹ est un noyau hétérocyclique saturé ou insaturé pentagonal ou hexagonal qui contient un, deux ou trois hétéro-atomes choisis entre des atomes d'oxygène, d'azote et de soufre, ce noyau hétérocyclique pouvant être un noyau

simple ou un noyau condensé à un noyau benzénique, et ce noyau hétérocyclique n'étant pas substitué ou portant ou un deux substituants halogéno, cyano ou amino, ou alkyle, alkoxy, alkylthio, alkylsulfinyle ou alkylsulfonyl ayant chacun jusqu'à 4 atomes de carbone, ou des substituants oxy ou hydroxy, ou qui peut porter, s'il est suffisamment saturé, un ou deux substituants oxo; et R^9 est un groupe phényle, naphthyle ou un noyau hétérocyclique tel que défini ci-dessus pour R^7 ou R^9 , caractérisé par:

(a) la réaction d'une amine de formule:

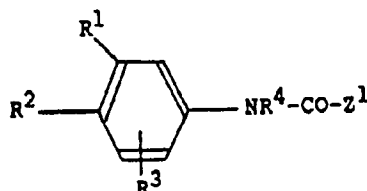


dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions indiquées, avec un acide de formule:

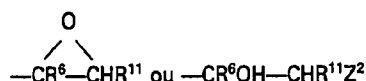


dans laquelle R^5 , R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus ou avec un dérivé réactif d'un tel acide; ou bien

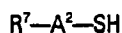
(b) pour la production d'un acylanilide dans lequel R^6 est un groupe hydroxy et X^1 est le soufre, la réaction d'un époxyde de formule:



dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions indiquées ci-dessus et Z^1 répond à la formule

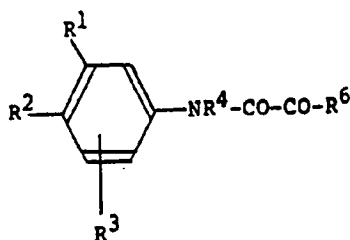


dans laquelle R^6 a la définition indiquée ci-dessus, Z^2 est un groupe déplaçable et R^{11} est choisi de manière que $-CHR^{11}-$ représente $-A^1-$ tel que défini ci-dessus, avec un thiol de formule:

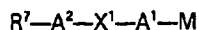


dans laquelle R^7 et A^2 ont les définitions données ci-dessus; ou

(c) pour la production d'un acylanilide dans lequel R^6 est un groupe hydroxy, la réaction d'un composé de formule:

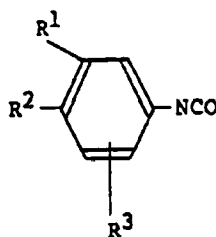


dans laquelle R^1 , R^2 , R^3 , R^4 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule:

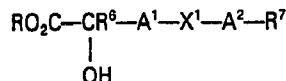


dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un métal alcalin; ou bien

(d) pour la production d'un acylanilide de l'invention dans lequel R⁴ et R⁵ forment conjointement un groupe carbonyloxy, la réaction d'un isocyanate de formule:



dans laquelle R¹, R² et R³ ont les définitions indiquées ci-dessus, avec un ester de formule:



dans laquelle R⁶, R⁷, X¹, A¹ et A² ont les définitions indiquées ci-dessus, et R est un groupe alkyle ayant jusqu'à 6 atomes de carbone; après quoi

(i) un acylanilide dans lequel R⁵ est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R⁵ est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel R⁵ est un groupe hydroxy et R⁴ est l'hydrogène peut être préparé par l'hydrolyse de l'oxazolidinedione correspondante, qui peut être préparée comme décrit dans le paragraphe (d) ci-dessus; ou bien

(iii) ou acylanilide dans lequel R⁴ est un groupe alkyle peut être préparé par alkylation de l'acylanilide correspondant dans lequel R⁴ est l'hydrogène; ou bien

(iv) un acylanilide dans lequel R⁵ est un groupe acyloxy peut être préparé par acylation de l'acylanilide correspondant dans lequel R⁵ est un groupe hydroxy; ou bien

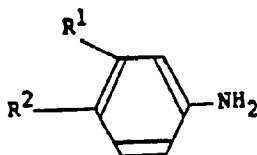
(v) une oxazolidinedione dans laquelle R⁴ et R⁵ forment conjointement un groupe carbonyloxy peut être préparée par réaction de l'acylanilide correspondant dans lequel R⁴ est l'hydrogène et R⁵ est un groupe hydroxy, avec le phosgène (COCl₂); ou bien

(vi) un acylanilide dans lequel X¹ ou X² est un groupe sulfinyle ou sulfonyle ou dans lequel un ou plusieurs de R¹, R² et un substituant du groupe phényle ou hétérocyclique R⁷, R⁸ ou R⁹, sont un groupe alkylsulfinyle, perfluoralkylsulfinyle ou phénylsulfinyle, ou un groupe alkylsulfonyle, perfluoralkylsulfonyle ou phénylsulfonyle, peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X¹ ou X² est le soufre ou dans lequel un ou plusieurs de R¹, R² et un substituant du groupe phényle ou hétérocyclique R⁷, R⁸ ou R⁹ sont, respectivement, un groupe alkylthio, perfluoralkylthio ou phénylthio; ou bien

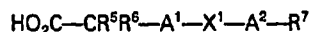
(vi) un acylanilide racémique dans lequel R⁵ est un groupe hydroxy peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéro-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

2. Procédé de production d'un acylanilide de formule suivant la revendication 1, dans laquelle R¹ est un groupe cyano, nitro, trifluorométhyle, chloro, méthyle ou méthoxy, R² est un groupe cyano, nitro, trifluorométhyle ou chloro, R³ et R⁴ sont tous deux de l'hydrogène, R⁵ est un groupe hydroxy, R⁶ est un groupe méthyle ou trifluorométhyle, A¹ est un groupe méthylène, éthylène ou éthylidène, X¹ est le soufre, un groupe sulfinyle ou sulfonyle, A² est une liaison directe ou un groupe méthylène et R⁷ est un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou un groupe phényle qui n'est pas substitué ou qui porte un substituant fluoro, chloro, cyano, nitro, méthoxy ou méthylthio, ou un groupe thiényl, imidazolyle, thiazolyle, benzothiazolyle, thiadiazolyle, pyridyle ou pyrimidinyle qui n'est pas substitué ou qui porte un substituant chloro, bromo ou méthyle, caractérisé par:

(a) la réaction d'une amine de formule:

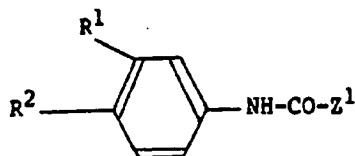


dans laquelle R¹ et R² ont les définitions indiquées ci-dessus, avec un acide de formule:

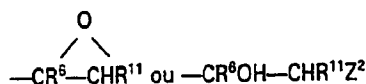


dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus et R^5 est un groupe hydroxy ou acyloxy tel que défini dans la revendication 1, ou avec un dérivé réactif dudit acide; ou bien

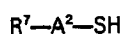
(b) pour la production d'un acylanilide dans lequel X^1 est le soufre, la réaction d'un époxyde de formule:



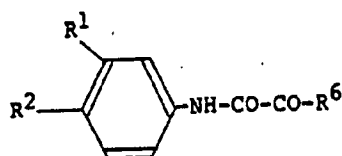
dans laquelle R^1 et R^2 ont les définitions indiquées ci-dessus et Z^1 répond à la formule



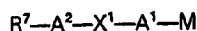
dans laquelle R^6 a la définition indiquée ci-dessus, Z^2 est un groupe déplaçable et R^{11} est choisi de manière que $\text{---CHR}^{11}\text{---}$ représente $\text{---A}^1\text{---}$ comme indiqué ci-dessus, avec un thiol de formule:



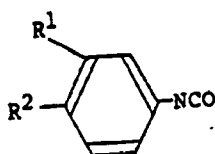
dans laquelle R^7 et A^2 ont les définitions indiquées ci-dessus; ou bien
(c) la réaction d'un composé de formule:



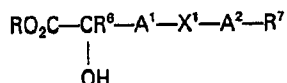
dans laquelle R^1 , R^2 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule:



dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un radical métallique; ou bien
(d) la réaction d'un isocyanate de formule:



dans laquelle R^1 et R^2 ont les définitions indiquées ci-dessus, avec un ester de formule:



dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus, et dans laquelle R est un groupe alkyle ayant jusqu'à 6 atomes de carbone, suivie de l'hydrolyse de l'oxazolidinedione ainsi obtenue; après quoi

(i) un acylanilide dans lequel R^5 est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R^5 est un groupe acyloxy; ou bien

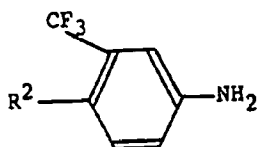
(ii) un acylanilide dans lequel X^1 est un groupe sulfinyle ou sulfonyle peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X^1 est le soufre; ou bien

(iii) un acide acylanilide racémique peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R^5 avec un acide optiquement actif, séparation des esters diastéro-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

3. Procédé de production d'un acylanilide de formule indiquée dans la revendication 1, dans laquelle R^1 est un groupe trifluorométhyle, R^2 est un groupe cyano ou nitro, R^3 et R^4 sont tous deux de l'hydrogène, R^5 est un groupe hydroxy, R^6 est un groupe méthyle, A^1 est un groupe méthylène, X^1 est le soufre, un groupe

sulfinyle ou sulfonyle, A² est une liaison directe et R⁷ est un groupe alkyle ayant jusqu'à 3 atomes de carbone, ou est un groupe allyle, phényle, *p*-fluorophényle, thiazole-2-yle, 4-méthylthiazole-2-yle, 5-méthyl-1,3,4-thiadiazole-2-yle ou 2-pyridyle, caractérisé par:

(a) la réaction d'une amine de formule:

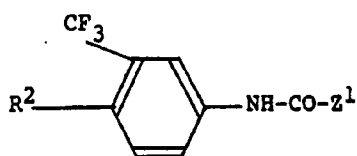


dans laquelle R², a la définition indiquée ci-dessus, avec un acide de formule:

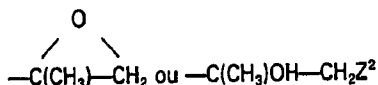


dans laquelle R⁷ et X¹ ont les définitions indiquées ci-dessus et R⁵ est un groupe hydroxy ou acyloxy comme indiqué dans la revendication 1, ou avec un dérivé réactif dudit acide; ou bien

(b) pour la production d'un acylanilide dans lequel X¹ est le soufre, la réaction d'un époxyde de formule:



dans laquelle R² a la définition indiquée ci-dessus et Z¹ répond à la formule

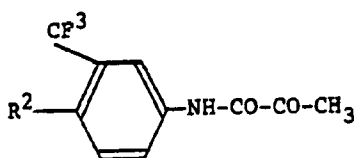


dans laquelle Z² est un groupe déplaçable, avec un thiol de formule:

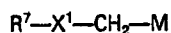


dans laquelle R⁷ a la définition indiquée ci-dessus; ou bien

(c) la réaction d'un composé de formule:



dans laquelle R² a la définition indiquée ci-dessus, avec un composé organométallique de formule:



dans laquelle R⁷ et X¹ ont les définitions indiquées ci-dessus et M est un radical métallique; après quoi
(i) un acylanilide dans lequel R⁵ est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R⁵ est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel X¹ est un groupe sulfinyle ou sulfonyle peut être préparé par oxydation de l'acylanilide correspondant dans lequel X¹ est le soufre; ou bien

(iii) un acylanilide racémique peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéréo-isomériques ainsi obtenus, puis hydrolyse en l'alcool de chaque ester séparé.

4. Procédé suivant la revendication 1, 2 ou 3, dans les matières de départ duquel R¹ est un groupe trifluorométhyle, R² est un groupe cyano, R³ et R⁴ sont chacun un atome d'hydrogène, R⁵ est un groupe hydroxy ou acyloxy, R⁶ est un groupe méthyle, A¹ est un groupe méthylène, X¹ est le soufre ou un groupe sulfonyle, A² est une liaison directe et R⁷ est un groupe *p*-fluorophényle, après quoi si R⁵ est un groupe acyloxy, le composé est hydrolysé en le composé correspondant dans lequel R⁵ est un groupe hydroxy, et si X¹ est le soufre, le composé est oxydé en le composé correspondant dans lequel X¹ est un groupe sulfonyle.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/042464 A1

(51) International Patent Classification⁷: C07C 205/11,
255/50, 323/25, C07D 213/74, A61K 31/04, 31/435,
31/277, 31/10, A61P 5/28

(74) Agents: BANNERMAN, David, Gardner et al.; With-
ers & Rogers, Goldings House, 2 Hays Lane, London SE1
2HW (GB).

(21) International Application Number:
PCT/GB2004/004464

(22) International Filing Date: 21 October 2004 (21.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0324551.1 21 October 2003 (21.10.2003) GB

(71) Applicant (for all designated States except US): KARO
BIO AB [SE/SE]; Novum, S-141 57 Huddinge (SE).

(71) Applicant (for MG only): ELSY, David [GB/GB]; With-
ers & Rogers, Goldings House, 2 Hays Lane, London SE1
2HW (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): JERNSTEDT,
Henrik [SE/SE]; Egilsgatan 13A, S-753 35 Uppsala (SE).
GARG, Neeraj [IN/SE]; Barkvägen 15, S-147 52 Tumba
(SE). GUSTAVSSON, Annika [SE/SE]; Koltrastvägen
26, S-178 39 Ekerö (SE). GILLNER, Mikael [SE/SE];
Renstiernas Gata 38, 3tr, S-116 31 Stockholm (SE).
GARCIA COLLAZO, Ana, Marla [—/SE]; Möregatan
10, 6tr, S-118 27 Stockholm (SE). KOCH, Eva [SE/SE];
Brunbärsvägen 8, S-114 21 Stockholm (SE).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

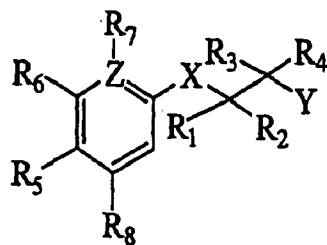
(81) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ANDROGEN RECEPTOR MODULATORS



(I)

(57) Abstract: Treatment of Diseases caused by Disturbances of the Activity of the Androgen Receptor uses of compounds of Formula (I): (as defined herein), for the treatment of diseases caused by disturbances of the activity of androgen receptor are provided: Formula (I). Isolated compounds of Formula (I) are also provided.

NOVEL COMPOUNDS

Field of Invention

This invention relates to novel compounds which are androgen receptor ligands, to methods of preparing such compounds and to methods for using such compounds such as for androgen hormone replacement therapy and for diseases modulated by the androgen receptor such as benign prostatic hyperplasia, prostate cancer, alopecia, hirsutism, bone loss, bone fractures, osteoporosis, cachexia, and muscle wasting.

Background of Invention

The androgen receptor (AR) is a member of the steroid hormone nuclear receptor family of ligand activated transcription factors. This group includes estrogen, progesterone, mineralocorticoid, and glucocorticoid receptors all of which are activated by endogenous steroid hormones to control the expression of responsive genes. The hormone receptors share a modular structure consisting of a variable amino-terminal domain (NTD), a highly conserved DNA-binding domain (DBD), and a carboxy-terminal ligand-binding domain (LBD). The DNA-binding domain generates much of the transcriptional specificity due to its ability to discern different DNA response elements with the promoter regions of target genes. The LBD is required for ligand dependent transcriptional activity containing both the hormone-binding pocket and an important transcriptional activation functional region (AF2) required for recruitment of coactivators and the cellular transcriptional machinery.

Regulation of nuclear receptor activity resides predominantly in the binding of the

hormone ligand within the LBD. The amino acids lining the interior of the hormone-binding cavity define the selectivity of the receptor for its hormone. This allows AR to discriminate between the natural ligands and non-natural ligands.

Another level of transcriptional control is conveyed by the nuclear receptor's environment. It is widely accepted that different effector proteins (coactivators and corepressors) exist within different cell types and can lead to different patterns of gene expression. Because the conformational state of the receptor dictates which coactivator is recruited in a given cell type, it also imparts transcriptional selectivity. It is precisely this type of control that gave rise to tissue selective receptor modulators. For example, tamoxifen is a prototypical estrogen receptor selective modulator with differing properties within breast and uterine tissues. Exploitation of the conformational changes induced by synthetic ligands within the hormone-binding cavity has led to multiple generations of tissue selective receptor modulators for the estrogen receptor and can be applied to developing modulators of other nuclear receptors such as the androgen receptor.

The use of natural and synthetic androgen in hormone replacement therapy has been shown to markedly decrease the risk of osteoporosis and muscle wasting. In addition, there is evidence that hormone replacement therapy has cardiovascular benefits. However hormone replacement therapy is also associated with an increase risk of prostate cancer. It is known that certain types of synthetic AR ligands display a mixed agonist/antagonist profile of activity showing agonist activity in some tissues and antagonist activity in other tissues. Such ligands are referred to as selective androgen receptor modulators (SARMS).

What is needed in the art are compounds that can produce the same positive responses as androgen replacement therapy without the negative side effects. Also needed are androgen-like compounds that exert selective effects on different tissues of the body.

The amino acids and the "space" they define as the hormone-binding cavity can be exploited in synthesizing modulators that are highly receptor selective. These interactions between the endogenous hormone and amino acid residues within the ligand-binding cavity induce conformational changes that are distributed throughout the entire receptor structure. It is these conformational changes that lead to the dissociation of chaperone proteins that stabilize the receptors in the absence of ligand and the association of coactivator proteins. A liganded receptor devoid of its chaperone proteins is able to dimerize, translocate, recruit coactivators, and initiate transcription.

The natural ligand for the androgen receptor, androgen, is produced in both men and women by the gonads, adrenal glands and locally in target tissues. The levels of androgens secreted by the gonads are tightly regulated by a feedback mechanism involving the hypothalamus and pituitary.

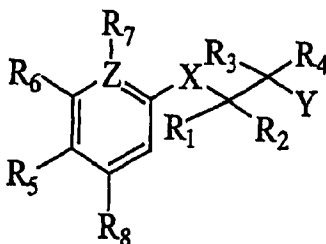
In men, androgens are necessary for masculinization and fertility. However, systemic androgen excess causes testicular atrophy and infertility. Androgens may also contribute to lipid abnormalities, cardiovascular disease and psychological abnormalities. Local androgen excess is implicated in the pathogenesis of male pattern baldness (alopecia), benign prostatic hyperplasia (BPH) and acne. The physiologic role of androgens in women is not well understood, but these steroids do play a role in the development of normal body hair and libido. In women, relative androgen excess causes hirsutism (excessive hair growth), amenorrhea (abnormal loss or suppression of menses), acne and male pattern baldness.

The risk of developing prostate cancer increases dramatically with age. More than 75% of prostate cancer diagnoses are in men over the age of 65, and the prevalence of clinically undetectable prostate cancer in men over 80 years old is as high as 80%. It remains unclear as to the exact cause of prostate cancer, however, it is widely accepted that androgens can increase the severity and the rate of progression of the disease.

Androgen deprivation therapy has been the basis for prostate cancer therapy since 1941 when castration was shown to have beneficial effects on advanced stages of the disease. Hormonal intervention is currently based on disrupting the hypothalamus-pituitary-gonadal feedback mechanism to control the levels of endogenous androgens from the testes. Antiandrogens are incorporated in later stage therapies to work at the level of the androgen receptor itself, blocking residual androgens from adrenal sources. In spite of these treatments, there exists a need for an improved therapy of diseases linked to disturbances in the activity of the androgen receptor.

SUMMARY OF THE INVENTION

The present invention provides the use of a compound according to Formula I for the preparation of a medicament, wherein Formula I is defined as:



Formula I

in which;

R₁ and R₂ are the same or different and independently selected from the group consisting of; hydrogen, halogen, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkenoxy, C₁-C₁₀ alkynoxy, C₁-C₁₀ alkylthio, C₁-C₁₀ alkenylthio, C₁-C₁₀ alkynylthio, C₆-C₁₀ arylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarylthio, C₁-C₁₀ alkylarylulphone, C₁-C₁₀ alkylarylulphoxide, C₆-C₁₀ aryl, or C₃-C₂₀ heteroaryl, optionally substituted with 0, 1, 2 or 3 groups of R¹ which groups may be the same or different; or R₁ and R₂ may together form a C₃-C₁₀ cycloalkyl group;

R₃ and R₄ are the same or different and independently selected from hydrogen, halogen, C₁-C₂₀ alkyl, C₃-C₇ cycloalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₄ alkoxy, C₁-C₄ alkenoxy, C₁-C₄ alkynoxy, C₁-C₄ alkylthio, C₁-C₄ alkenylthio, C₁-C₄ alkynylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarylthio, C₁-C₁₀ alkylarylsulphone, C₁-C₁₀ alkylarylsulphoxide, C₆-C₁₅ aryl, C₅-C₂₀ heteroaryl optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different; or can together form a keto group;

R₅ is chosen from the group consisting of; nitro, cyano, -CH₂CN, -COMe, acetic acid, halogen, sulphonic acid, -SO₂CH₃, aldehyde, carboxylic acid or ester, phosphonic acid or ester;

R₆ is chosen from the group consisting of; hydrogen, C₁-C₅ alkyl, halogen, CN, CO₂H, CHF₂, CH₂F or CF₃;

R₇ is chosen from the group consisting of; H, halogen or C₁-C₅ alkyl;

R₈ is chosen from the group consisting of; hydrogen, C₁-C₅ alkyl, halogen, CHF₂, CH₂F or CF₃;

X is chosen from the group consisting of; -NH-, -O-, -S-, -SO-, -SO₂-, -Se-, -Te- or -S-S-

Y is chosen from the group consisting of; hydrogen, hydroxy, -CH₂OH, methoxy, NH₂, unbranched, branched or cyclic C₁-C₅ alkyl, unbranched, branched or cyclic -NH(C₁-C₅); unbranched, branched or cyclic N(C₁-C₅)₂, -NH(C₆aryl), -N(C₆aryl)₂, -NH(C₁-C₁₀ heteroaryl), and -N(C₅-C₁₀ heteroaryl)₂, C₅-C₁₀ heteroaryl wherein any of said aryl or heteroaryl groups are optionally substituted with up to 3 groups of R^a which groups may be the same or different;

Z is chosen from the group consisting of; C, N, or O;

R^a represents a member selected from: hydrogen, halogen, -CN, OH, CO_2H , CHO, NO_2 , $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{C}_4)$, $\text{N}(\text{C}_1\text{C}_4)_2$, $-\text{NH}(\text{C}_6\text{aryl})$, $-\text{N}(\text{C}_6\text{aryl})_2$, $-\text{NH}(\text{C}_5\text{C}_{10}\text{ heteroaryl})$, and $-\text{N}(\text{C}_5\text{C}_{10}\text{ heteroaryl})_2$; or a pharmaceutically acceptable salt thereof.

A preferred compound is according to formula I, wherein R_1 or/and R_2 are H, (S)-methyl, methyl, (R)-ethyl, (S)-ethyl, ethyl, (R)-propyl, (S)-propyl, propyl, (S)-butyl, (S)-1-methyl-propyl, (S)-2-methyl-propyl, (R)-isopropyl, (S)-isopropyl, isopropyl, cyclopentyl, $-(\text{CH}_2)_2\text{SMe}$, (R)- $\text{CH}_2\text{SCH}_2\text{Ph}$, (S)-benzyl, 4-chloro-benzyl, (S)-3-methyl-1-H-indole or (S)-phenyl;

Further preferred is a compound according to formula I, wherein R_3 is chosen from the group consisting of: hydrogen, methyl, ethyl, phenyl, 3-hydroxy phenyl, 4-hydroxy phenyl, or forms a keto group together with R_4 .

Further preferred is a compound according to formula I, wherein R_4 is H, methyl, or forms a keto group together with R_3 .

Further preferred is a compound according to formula I, wherein R_5 is NO_2 , CN, CH_2CN or CO_2H ;

Further preferred is a compound according to formula I, wherein R_6 is Me, or CF_3 ;

Further preferred is a compound according to formula I, wherein R_7 is H or Me;

Further preferred is a compound according to formula I, wherein R_8 is H or methyl;

Further preferred is a compound according to formula I, wherein X is NH;

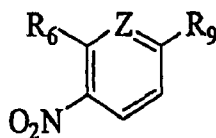
Further preferred is a compound according to formula I, wherein Y is H, -OH, -OMe, -N(CH₂CH₃)₂, piperidine, or 4-nitro-2-ylamino;

Further preferred is a compound according to formula I, wherein Z is CR₇ or N;

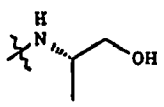
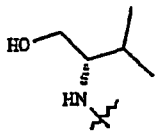
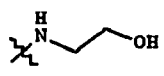
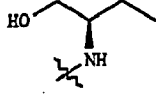
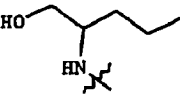
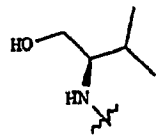
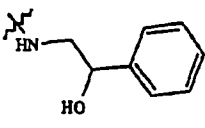
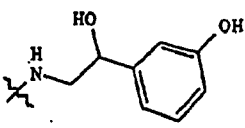
Even more preferred is a compound according to formula I, chosen from the group consisting of;

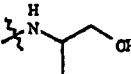
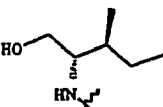
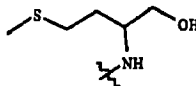
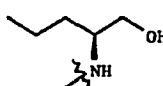
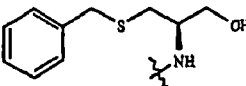
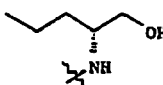
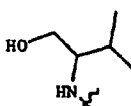
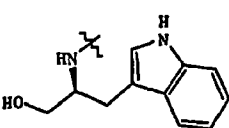
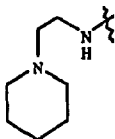
2-Methyl-2-(4-nitro-3-trifluoromethyl-phenylamino)-propan-1-ol;
[1-(4-Nitro-3-trifluoromethyl-phenylamino)-cyclopentyl]-methanol;
(S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-3-phenyl-propan-1-ol;
(S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-butan-1-ol;
2-Methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol;
[1-(3-Methyl-4-nitro-phenylamino)-cyclopentyl]-methanol;
(S)-2-(3-Methyl-4-nitro-phenylamino)-butan-1-ol;
[1-(6-Methyl-5-nitro-pyridin-2-ylamino)-cyclopentyl]-methanol;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-2-phenyl-ethanol;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenyl-propan-1-ol;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-butan-1-ol;
(DL)-3-(4-Chloro-phenyl)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol;
(S)-2-(6-Methyl-5-nitro-2-pyridin-2-ylamino)-propionic acid;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol;
2-(2,3-Dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol;
(S)-2-(3,5-Dimethyl-4-nitro-phenylamino)-butan-1-ol;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-benzonitrile;
4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
(S)-4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
(R)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;

(S)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;
[4-((S)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
[4-((R)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
[4-((S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile;
6-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-nicotinonitrile;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile;
and the compounds showed in the following table (The substituents, R₉, R₆, and Z, are shown in the table, and are all substituents in the following formula II. In formula II, the NO₂ group corresponds to the substituent R₅ in formula I, and R₉ is composed of the moieties XR₁R₂YR₃R₄ of Formula I as defined above, where X is -NH-

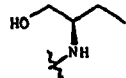
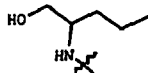
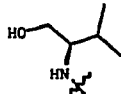
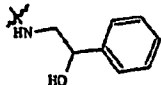
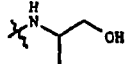
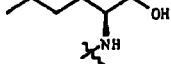
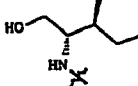
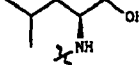
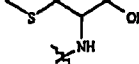


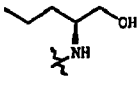
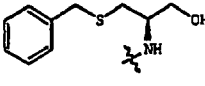
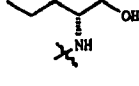
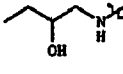
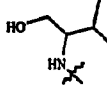
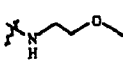


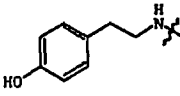
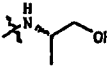
Formula II

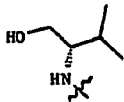
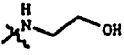
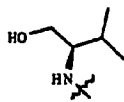
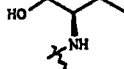
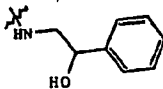
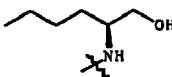
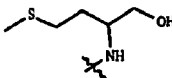
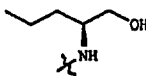
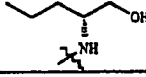
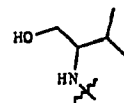
R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH

R9	R6	Z		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		

R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	CH

R9	R6	Z		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		

2, 2-Dimethyl-3-(3-methyl-4-nitro-phenylamino)-propan-1-ol

4-((R)-1-Benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

(R)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenylmethanesulfinyl-propan-1-ol

4-((R)-2-Hydroxy-1-phenylmethanesulfinylmethyl-ethylamino)-2-trifluoromethyl-benzonitrile

[1-(4-Nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(4-Nitro-phenylamino)-pentan-1-ol

(S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol

[1-(2-Bromo-4-nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(2-Bromo-4-nitro-phenylamino)-pentan-1-ol

(S)-2-(2-Bromo-4-nitro-phenylamino)-4-methyl-pentan-1-ol

or a pharmaceutically acceptable salt thereof.

Also preferred is a compound according to Formula I, wherein R_1 or R_2 is a C_6-C_{10} arylthio moiety comprising an aryl-substituted sulfur-containing C_1-C_{10} alkyl group.

Further preferred is a compound according to Formula I, wherein in R_1 or R_2 the alkylsulfur is substituted with a C_6 aryl group.

The present invention further provides a pharmaceutical composition which contains one or more of the compounds according to the above.

More preferred is a pharmaceutical composition according to the above, for use as a medicament.

Furthermore, the invention provides the use of a pharmaceutical composition according to the above for manufacturing a medicament to be used in the treatment of a disease caused by a disturbance in the activity of the androgen receptor.

Since the compounds are shown to be mainly antagonists for the androgen receptor, a preferred use is the use of the composition above for treating a disease which is caused by an increase in androgen receptor activity.

Even more preferred is the use of the composition above for treating a disease which is chosen from the group consisting of: prostate cancer, lipid abnormalities, cardiovascular disease and psychological abnormalities, male pattern baldness (alopecia), benign prostatic hyperplasia (BPH) and acne, hirsutism, amenorrhea, hypogonadism, anemia, diabetes, defects in spermatogenesis, cachexia, osteoporosis, osteopenia, and muscle wasting.

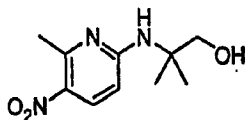
The present invention also provides the use of a compound according to the above for manufacturing a medicament to be used in the treatment of a disease caused by a disturbance in the activity of the androgen receptor.

A specific disease that would be amenable for treatment by the present invention is a disease chosen from the group consisting of: prostate cancer, lipid abnormalities, cardiovascular disease and psychological abnormalities, male pattern baldness (alopecia), benign prostatic hyperplasia (BPH) and acne, hirsutism, amenorrhea, hypogonadism, anemia, diabetes, defects in spermatogenesis, cachexia, osteoporosis, osteopenia, and muscle wasting.

Methods of treating such diseases by administering a therapeutically effective amount of such compounds to a patient are also provided by the invention.

The compounds of the present invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s) active in the therapeutic areas described herein.

According to another aspect of the invention there is provided a compound as defined in Formula I, provided that the compound is not the compound according to the formula;



The specific compound above is known in the prior art as an intermediate compound in the manufacture of compounds used in different technical fields, namely the dye industry (Compound Reference: Specs and Bio Specs B.V.; Catalog No. AK-079/11126007).

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "androgen receptor ligand" as used herein is intended to cover any moiety, which binds to an androgen receptor. The ligand may act as an antagonist, or as a partial antagonist.

A compound being a "partial antagonist" is a compound with both agonistic and antagonistic activity.

The term "alkyl" as employed herein alone or as part of another group refers to an acyclic straight or branched chain radical, containing 1 to about 10 carbons, preferably 1 to 6 carbons in the normal chain, i.e. methyl, ethyl, propyl, isopropyl, sec-butyl, tert-butyl, pentyl, hexyl, octyl. When substituted alkyl is present, this refers to an unbranched or branched alkyl group, which groups may be the same or different at any available point, as defined with respect to each variable.

The term "substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which are commonly attached to such chains, such as, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino, halo, carboxyl or alkyl ester thereof and/or carboxamide.

The term "alkenyl" as employed herein alone or as part of another group refers to a straight or branched chain radical, containing 2 to about 10 carbons, preferably 2 to 6 carbons i.e. ethenyl, propenyl, butenyl, allyl.

The term "allyl" refers to $\text{H}_2\text{C}=\text{CH}-\text{CH}_2$.

The term "alkynyl" as employed herein alone or as part of another group refers to a straight or branched chain radical, containing 2 to about 10 carbons, preferably 2 to 6 carbons i.e. ethynyl, propynyl, butynyl, allyl.

The term "aryl" as employed herein alone or as part of another group refers to substituted and unsubstituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polycyclic aromatic ring system and polyaromatic ring systems. The polycyclic aromatic and polyaromatic ring systems may contain from two to four, more preferably two to three rings. Preferred aryl groups include 5- or 6- membered ring systems.

The term "heteroaryl" refers to optionally substituted aromatic ring system having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl includes five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring system and polyheteroaromatic ring systems. The poly heterocyclic aromatic and poly heteroaromatic ring systems may contain from two to four, more preferably two to three rings. The term hetero aryl includes ring system such as pyridine, quinoline, furan, thiophene, pyrrole, imidazole and pyrazole.

The term "alkoxy" as employed herein alone or as part of another group refers to an alkyl ether wherein the term alkyl is as defined above. Examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

The term "aryloxy" as employed herein alone or as part of another group refers to an aryl alkyl ether, wherein the term aryl is as defined above. Examples of aryloxy radicals include phenoxy, benzyloxy and the like.

The term "alkylthio" as employed herein alone or as part of another group refers to an alkyl thio wherein the term alkyl is as defined above and one of the methylene carbons has been replaced with sulfur. Examples of alkylthio radicals include methane thiol, ethane thiol, propane thiol, $-(CH_2)_m S(CH_2)_n$, where $m + n = 9$ and the like.

The term "alkylsulphone" as employed herein alone or as part of another group refers to an alkylsulphone wherein the term alkyl is as defined above and one of the methylene carbons has been replaced with sulfur. Examples of alkylsulphone radicals include methanesulphone, ethanesulphone, propanesulphone, $-(CH_2)_m SO_2(CH_2)_n$, where $m + n = 9$ and the like.

The term "alkylsulphoxide" as employed herein alone or as part of another group refers to an alkylsulphoxide wherein the term alkyl is as defined above and one of the methylene carbons has been replaced with sulfur. Examples of alkylsulphoxide radicals include methanesulphoxide, ethanesulphoxide, propanesulphoxide $-(CH_2)_m SO(CH_2)_n$, where $m + n = 9$ and the like.

The term "alkylarylthio" as employed herein alone or as part of another group refers to an arylalkylthio wherein the term alkylthio and aryl are as defined above and one of the terminal methyl groups is substituted with aryl. Examples of $-(CH_2)_m S(CH_2)_n CH_2-Ar$ where $m + n = 8$ and the like.

The term "alkylarylsulphone" as employed herein alone or as part of another group refers to an arylalkylsulphone wherein the term alkylsulphone and aryl are as defined above and one of the terminal methyl groups is substituted with aryl. Examples of $-(CH_2)_m SO_2(CH_2)_n CH_2-Ar$ where $m + n = 8$ and the like.

The term "alkylarylsulphoxide" as employed herein alone or as part of another group refers to an arylalkylsulphoxide wherein the term alkylsulphoxide and aryl are as defined above and one of the terminal methyl groups is substituted with aryl. Examples of $-(CH_2)_m SO(CH_2)_n CH_2-Ar$ where $m + n = 8$ and the like.

The term "cycloalkyl" as employed herein alone or as part of another group refers to saturated cyclic hydrocarbon groups or partially unsaturated cyclic hydrocarbon groups, independently containing one carbon-to-carbon double bond. The cyclic hydrocarbon contains 3 to 4 carbons. It should also be understood that the present invention also involve cycloalkyl rings where 1 to 2 carbons in the ring are replaced by either -O-, -S- or -N-, thus forming a saturated or partially saturated heterocycle. Examples of such rings

are aziridine, thiiranes and the like. Preferred heterocyclic rings are 3-membered, which may be optionally substituted by 1, 2 or 3 groups of R^a which groups may be the same or different through available carbons as in the case of "alkyl". Preferred cycloalkyl groups include 3 carbons, such as cyclopropyl, which may be optionally substituted by 1, 2 or 3 groups of R^a which groups may be the same or different through available carbons as in the case of "alkyl".

The term "halogen" refers to fluorine, chlorine, bromine and iodine. Also included are carbon substituted halogens such as $-CF_3$, $-CHF_2$, and $-CH_2F$

The compounds of the present invention can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of the invention have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of the invention having at least one acid group (e.g. $COOH$) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine,

piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts that are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of the invention or their pharmaceutically acceptable salts, are also included. Preferred salts of the compounds of the present invention which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. Preferred salts of the compounds of formula I which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

The compounds according to the invention may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention. Such prodrugs are well known in the art and a comprehensive description of these may be found in: (i) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996); (ii) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and (iii) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 – 191 (Harwood Academic Publishers, 1991).

Embodiments of prodrugs suitable for use in the present invention include lower alkyl esters, such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM).

The compounds according to the present invention are preferably administered in a therapeutically effective amount. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein.

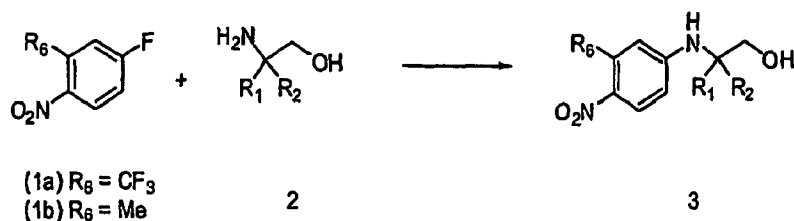
The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration.

Scheme 1-6 outlines the synthetic routes used for preparing the compound according to Formula I

Scheme 1

Synthetic routes to these compounds can be visualized by the skilled person and the present synthetic route is not limiting for the invention. 4-Fluoro-1-nitro-2-trifluoromethyl-benzene (1a) and 4-fluoro-2-methyl-1-nitro-benzene (1b) were employed as starting material in scheme-1 and is commercially obtainable.

Scheme 1 depicts a synthesis of compounds of formula I in which R_6 is CF_3 and Me and is connected to phenyl ring. Condensation of compound (1a) with different β -amino alcohols and di-isopropyl ethylamine in DMSO gave compound 3 (examples 1-4) in quantitative yield. The reactions were performed in a microwave oven at elevated temperature for a short time. Compound (1b) was used for producing the compound 3 (examples 5-7) and similar conditions were adopted as in examples 1-4. An alternative method was used for the preparation of example-5. The reaction according to the alternative method was performed by heating the compound (1b) and β -amino alcohol in pentanol in a sealed tube.

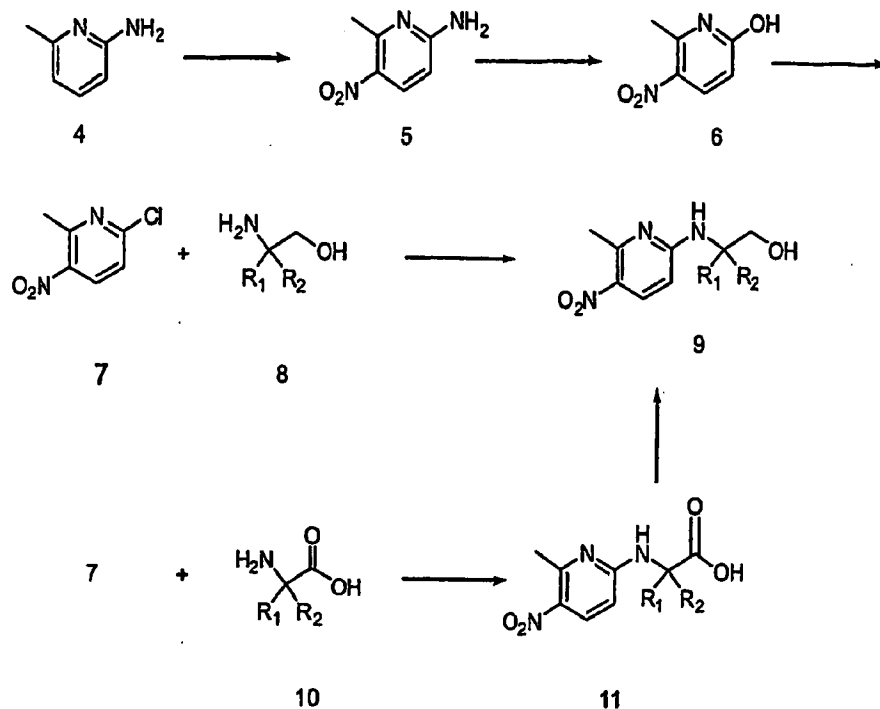


Scheme 1

Scheme 2

Compounds 9 (examples 8-15) were prepared from starting material 6-chloro-3-nitro-2-picoline (compound 4). Starting material was synthesized in three steps starting with compound 6-amino-2-picoline using the literature procedure. Nitration of 6-amino-2-picoline was accomplished by concentrated sulphuric acid (H_2SO_4) and concentrated nitric acid (HNO_3) and provided 6-amino-3-nitro-2-picoline (Baumgarten, H. E. and Chien Fan Su, H. *JACS* 74 (1952) 3828; Parker, E. D. and Shive, W. *JACS* 69 (1947) 63). Treatment of 6-amino-3-nitro-2-picoline with sodium nitrite provided 6-hydroxy-3-nitro-2-picoline, which, when reacted with PCl_5 and POCl_3 , provided 6-chloro-3-nitro-2-picoline (Baumgarten, H. E. and Chien Fan Su, H. *JACS* 74 (1952) 3828).

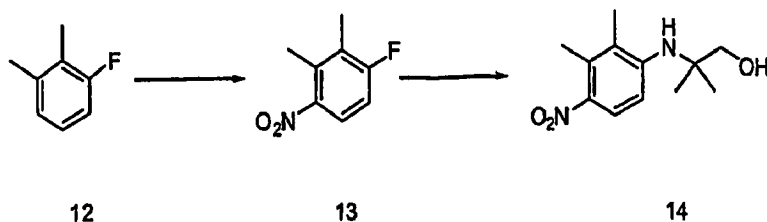
Scheme 2 shows the synthesis of compounds of formula I in which Z is N and R_3 is H. Condensation of 6-Chloro-3-nitro-2-picoline and 2-amino-2-methyl-propan-1-ol in 1-pentanol and the mixture refluxed under inert atmosphere gave compound 9 (example-8) as yellow crystals. 6-Chloro-3-nitro-2-picoline can also be purchased as commercial starting material. The reaction time was reduced by using a microwave oven. Condensation of compound 7 with different β -amino alcohols (8) in the microwave provided compound 9 (examples 9-13) in quantitative yield. Synthetic routes to these compounds can be visualized by the skilled person. Reaction of compound (10) with L-alanine provided compound 11 (example-14). Reduction of the acid compound (11) by a reducing agent such as lithium aluminum hydride (LAH) produced compound 9 (example 15).



Scheme 2

Scheme 3

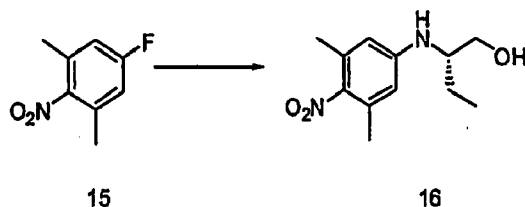
Synthesis of compounds according to formula I, in which R_6 and R_7 are Me and connected to the phenyl ring is shown in Scheme-3. 4-Fluoro-2, 3-di-methyl-1-nitro-benzene (13) was employed as starting material in scheme-3, which was produced by the nitration of compound (12) with fuming nitric acid in acetic anhydride in one step. Condensation of 2, 3-dimethyl-fluoro-benzene with β -amino alcohols at higher temperature gave compound 14 (example 16).



Scheme 3

Scheme 4

Scheme 4 depicts a synthesis of compounds of formula I in which R_6 and R_8 are Me and connected to the phenyl ring. Condensation of compound (15) with (S)-2-amino-butan-1-ol and di-isopropyl ethylamine in DMSO gave compound 16 (examples 17). The reaction was performed in a microwave oven.

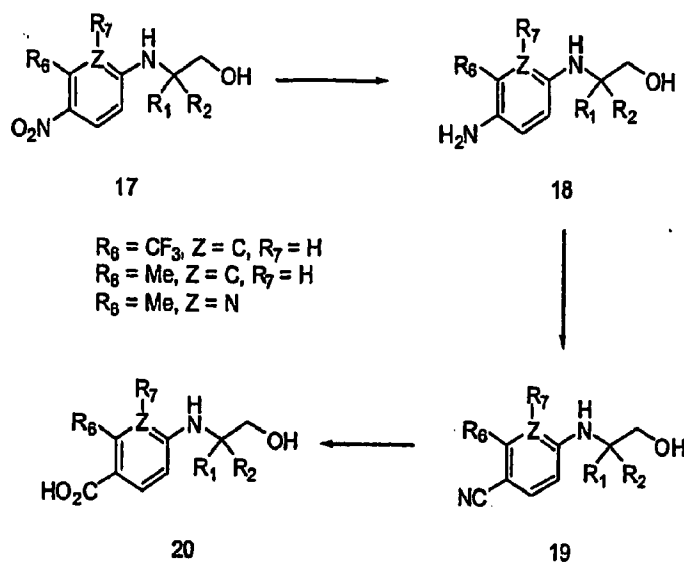


Scheme 4

Scheme 5

Reduction of nitro compound to amine was accomplished by the treatment of sodium thiosulphate with ethanol. After work-up the amines were used for the next step without any further purification. Reaction of amine with potassium cyanide and copper cyanide in water gave compound 19 (examples 26-28). (Clive, D. L. *et al. JOC* 52 (1987) 1339-42 and Vogel expt. 6.76). Some other examples of compound 19 were made by an alternative method utilizing a microwave oven. Similar reaction conditions as those used in scheme-1 and scheme-2 provided compound 19 (examples 18-22).

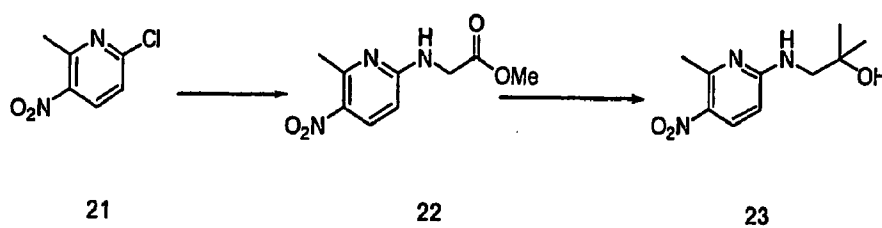
Conversion of the nitrile form of compound 19 to benzoic acid compound 20 (example 87) was performed in a refluxed aqueous sodium hydroxide solution in methanol.



Scheme 5

Scheme 6

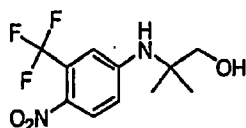
Scheme 6 depicts a synthesis of compounds of formula I in which R_3 and R_4 are Me and is connected to the alkyl chain. Condensation of 6-chloro-3-nitro-2-picoline with glycine methyl ester hydrochloride and triethyl amine in DMSO gave compound 22 (example 88). Compound 22 was treated with methyl magnesium bromide and after HPLC purification gave compound 23 (example 89).



Scheme 6

EXAMPLES

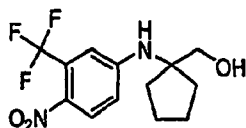
The following Examples represent preferred embodiments of the present invention. However, they should not be construed as limiting the invention in any way. The ^1H NMR spectra were consistent with the assigned structures. Mass spectra were recorded on a Perkin-Elmer, API 150Ex spectrometer, with turbo "ion spray" on negative ion mode (ES-1) or positive (ES+1), using a Zorbax SB-C8 column (LC-MS). The microwave reactions were performed in a Personal Chemistry Emrys Optimizer.

Example 12-Methyl-2-(4-nitro-3-trifluoromethyl-phenylamino)-propan-1-ol

4-Fluoro-1-nitro-2-trifluoromethyl-benzene (1.226 g, 5.86 mmol) was dissolved in 7 mL DMSO and 2-amino-2-methyl-propan-1-ol (784 mg, 8.795 mmol) was added, followed by diisopropyl ethylamine (DIPEA) (985 mg, 7.622 mmol). The reaction was heated to 180 °C for 900 seconds in a microwave oven (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The mixture was diluted with 20 mL of EtOAc and then washed three times with an aqueous solution of ammonium chloride (NH_4Cl). The organic phase was collected, dried with MgSO_4 (anhydrous) and filtered. The dry organic phase was evaporated *in vacuo*. The crude product was a bright yellow powder. The crude product was purified on a silica column with 5:1 n-heptane: EtOAc as mobile

phase. This gave 1.1 g (68 %) of 2-methyl-2-(4-nitro-3-trifluoromethyl-phenylamino)-propan-1-ol as a yellow solid. $M/Z = 278$

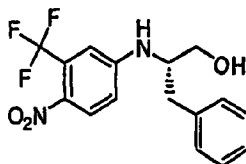
Example 2



[1-(4-Nitro-3-trifluoromethyl-phenylamino)-cyclopentyl]-methanol

4-Fluoro-1-nitro-2-trifluoromethyl-benzene (122 mg, 0.583 mmol) was coupled with (1-amino-cyclopentyl)-methanol (101 mg, 0.875 mmol), DIPEA (90.5 mg, 0.700 mmol) in DMSO 0.8 mL, using the same procedure as described in Example-1. This gave 120.5 mg (68%) of [1-(4-nitro-3-trifluoromethyl-phenylamino)-cyclopentyl]-methanol as a yellow powder. $M/Z = 304$.

Example 3

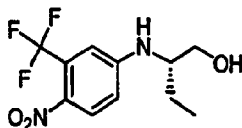


(S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-3-phenyl-propan-1-ol

4-Fluoro-1-nitro-2-trifluoromethyl-benzene (119 mg, 0.569 mmol) was coupled with (S)-2-amino-3-phenyl-propan-1-ol (129 mg, 0.854 mmol), DIPEA (88 mg, 0.683 mmol) in DMSO 0.8 mL using the same procedure as described in Example-1. This gave 112 mg

(58%) of (S)-2-(4-nitro-3-trifluoromethyl-phenylamino)-3-phenyl-propan-1-ol as yellow crystals. $M/Z = 340$.

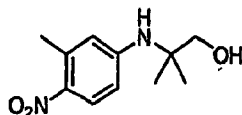
Example 4



(S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-butan-1-ol

4-Fluoro-1-nitro-2-trifluoromethyl-benzene (122 mg, 0.583 mmol) was coupled with (S)-2-amino-butan-1-ol (78 mg, 0.875 mmol), DIPEA (91 mg, 0.700 mmol) in DMSO 0.8 mL using the same procedure as described in Example-1. This gave 107 mg (67%) of (S)-2-(4-nitro-3-trifluoromethyl-phenylamino)-butan-1-ol as yellow oily crystals. $M/Z = 278$.

Example 5

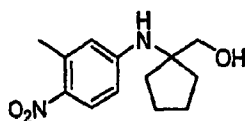


2-Methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol

Method-A: 4-Fluoro-2-methyl-1-nitro-benzene (113 mg, 0.728 mmol) was coupled with 2-amino-2-methyl-propan-1-ol (84 mg, 0.947 mmol), DIPEA (122 mg, 0.947 mmol) in DMSO 1.2 mL using the same procedure as described in Example-1. The crude product was purified on a silica column with 1:1 n-heptane: EtOAc as mobile phase. This gave 72 mg (44 %) of 2-methyl-2-(3-methyl-4-nitro-phenylamino)-propan-1-ol as yellow powder. $M/Z = 224$.

Method-B: 4-Fluoro-2-methyl-1-nitro-benzene (2.33 g, 15 mmol) and 2-amino-2-methylpropanol (2.67 g, 30 mmol) were heated with stirring at 160°C in a sealed tube overnight. The reaction mixture was diluted with EtOAc and purified by flash chromatography (dry application; 14% EtOAc in hexane → EtOAc) to afford 2.85 g (85%) of the 2-methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol.

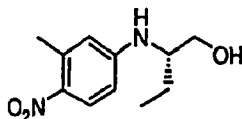
Example 6



[1-(3-Methyl-4-nitro-phenylamino)-cyclopentyl]-methanol

4-Fluoro-2-methyl-1-nitro-benzene (107 mg, 0.689 mmol) was coupled with (1-amino-cyclopentyl)-methanol (103 mg, 0.897 mmol), DIPEA (116 mg, 0.897 mmol) in DMSO 1.2 mL using the same procedure as described in Example-1. The crude product was purified on a silica column with 1:1 n-heptane: EtOAc as mobile phase. This gave 76 mg (44 %) of [1-(3-methyl-4-nitro-phenylamino)-cyclopentyl]-methanol as a yellow powder. M/Z = 250.

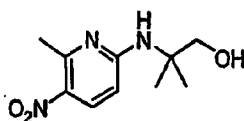
Example 7



(S)-2-(3-Methyl-4-nitro-phenylamino)-butan-1-ol

4-Fluoro-2-methyl-1-nitro-benzene (102 mg, 0.658 mmol) was coupled with (S)-2-amino-butan-1-ol (76 mg, 0.855 mmol), DIPEA (111 mg, 0.855 mmol) in DMSO 1.2 mL using the same procedure as described in Example-1. The crude product was purified on a silica column with 1:1 n-heptane: EtOAc as mobile phase. This gave 85 mg (58 %) of (S)-2-(3-methyl-4-nitro-phenylamino)-butan-1-ol as yellow oil. $M/Z = 224$.

Example 8



2-Methyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

(a) Conc. H_2SO_4 (140 ml) was cooled in an ice-salt bath and molten 6-amino-2-picoline (30 g, 0.277 mol) was added in portions with good stirring. To this brown, viscous solution which was maintained at $0^\circ C$ was added a cooled ($0^\circ C$) mixture of conc. H_2SO_4 (21 ml) and conc. HNO_3 (21 ml) drop wise over a period of approx. 1.5 hrs. The red-orange reaction mixture was stirred for an additional hour at $0^\circ C$ and then allowed to warm slowly to room temperature over night. The brown solution was heated at $60^\circ C$ (oil bath) for 1 hr followed by 1 hr at $100^\circ C$ (carefully controlled temperature). The reaction mixture was cooled to $0^\circ C$ (ice bath), poured over cracked ice and neutralised by addition of a concentrated aqueous NaOH solution. The yellow precipitate was filtered and washed well with ice-water. (The filtrate was put in the refrigerator; additional product was precipitated together with the salts.) The yellow product was suspended in water and divided into two portions, each of them subjected to steam distillation in turn. The yellow reaction mixture became more "transparent" after some hrs, but the collected steam, containing 4-amino-3-nitro-2-picoline, was still yellow after 6 hrs. The steam distillation was stopped after 8 hrs, the residual part of the reaction mixture was filtered and

evaporated to dryness. ¹HNMR (D₂O) showed a mixture of 2-3 compounds. The mixture was washed with: CHCl₃, EtOH (x 2) and CHCl₃ leaving 20.4 g (48%) of pure 6-amino-3-nitro-2-picoline.

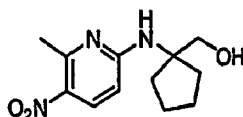
(b) 6-Amino-3-nitro-2-picoline (20 g, 0.131 mol) was suspended in a mixture of conc. H₂SO₄ (23.7 ml) and water (335 ml). More conc. H₂SO₄ (20 ml) was added under ice-cooling, but the amine did not dissolve completely. The suspension was added in ice (100 g) before a solution of NaNO₂ (13.53 g, 0.196 mol) in water (40 ml) was added drop wise. Gas evolution was observed. The brown suspension was stirred at 10°C for 1 hr, filtered and washed with water. The brown product was dried (freeze dryer) to achieve 15.78 g (78 %) of 6-hydroxy-3-nitro-2-picoline.

(c) To 6-Hydroxy-3-nitro-2-picoline (15.73 g, 0.102 mol) was added PCl₅ (5.73 g, 0.027 mol) and POCl₃ (2.9 ml, 0.032 mol). This mixture was heated at 110-115°C for 3 hrs. However, the amount of POCl₃ added was only enough to moisten the starting material. More POCl₃ (3 ml) was added, the reaction mixture heated at 110-115°C but only sublimation of PCl₅ (100°C) was observed. DMF (5 ml) was added and the solution was heated at 115°C for 5 hrs, cooled and poured into a slush of ice and water. A beige product precipitated and the water suspension was stirred for 48 hrs. The brown precipitate was filtered off and washed with water. Purification by dry-flash dichloromethane yielded 10.93 g (62 %) of 6-chloro-3-nitro-2-picoline.

(d) 6-Chloro-3-nitro-2-picoline (6.055 g, 35.1 mmol) and 2-amino-2-methyl-propan-1-ol (6.2 g, 73.7 mmol) were suspended in 1-pentanol (30 ml) and the mixture refluxed under inert atmosphere overnight. The thin layer chromatography (dichloromethane 4/EtOAc 1) revealed some remaining starting material, so the reaction was refluxed for another 3.5 hrs. The reaction mixture was cooled and water was added under stirring. A sticky, yellow precipitate was filtered off, washed well with water and dried. The crude product (6.04 g) was re-crystallised from either pentane-acetone or dichloromethane. Collecting

the crops furnished 5.71 (72 %) of 2-methyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol as yellow crystals. $M/Z = 225$.

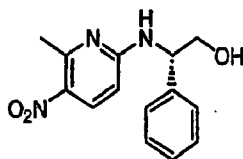
Example 9



[1-(6-Methyl-5-nitro-pyridin-2-ylamino)-cyclopentyl]-methanol

6-Chloro-3-nitro-2-picoline (22 mg, 0.13 mmol) was coupled with (1-amino-cyclopentyl)-methanol (31 mg, 0.27 mmol), triethylamine (0.025 mL, 0.18 mmol) in 2-pentanol (1 mL). The reaction was heated to 180 °C for 2 h in a microwave oven (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The mixture was diluted with 20 mL of EtOAc and then washed with NaHCO₃. The organic phase was collected, dried with anhydrous MgSO₄ and filtered. The dry organic phase was evaporated and purified on a silica column with 5:1 n-Heptane: EtOAc as mobile phase. This gave 9 mg (28%) of [1-(6-methyl-5-nitro-pyridin-2-ylamino)-cyclopentyl]-methanol as a yellow solid. $M/Z = 251$

Example 10



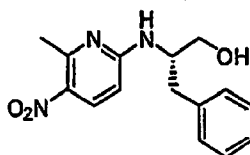
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino) 2-phenyl-ethanol

6-Chloro-3-nitro-2-picoline (22 mg, 0.13 mmol) was coupled with (2-amino-2-phenyl)-

propanol (34 mg, 0.25 mmol) in triethylamine (0.030 mL, 0.25 mmol) in DMSO (1 mL).

The reaction was heated to 140 °C for 1200 seconds in a microwave oven (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The mixture was diluted with 20 mL of EtOAc and then washed with NH₄Cl (aq) three times. The organic phase was collected, dried with anhydrous MgSO₄ and filtered. The dry organic phase was evaporated and purification on silica column with 5:1 n-Heptane: EtOAc gave 22 mg (63%) of (R)-2-(6-methyl-5-nitro-pyridin-2-ylamino) 2-phenyl-ethanol as a yellow solid. $M/Z = 273$.

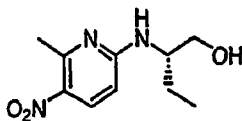
Example 11



(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenyl-propan-1-ol

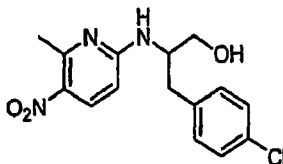
6-Chloro-3-nitro-2-picoline (30 mg, 0.17 mmol) was coupled with (S)-2-amino-3-phenyl-propan-1-ol (32 mg, 0.21 mmol), sodium acetate (28 mg, 0.34 mmol) in EtOH (2 mL).

The reaction was heated in a microwave oven for 20 min at 130 °C and then additionally 20 minutes at 150 °C. The reaction was quenched with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc and evaporated. Purification on a silica column with a gradient solution of heptane: EtOAc gave 24 mg (48%) of (S)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-3-phenyl-propan-1-ol as a yellow solid. $M/Z = 287$.

Example 12

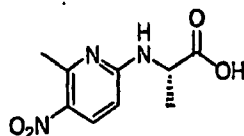
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-butan-1-ol

6-Chloro-3-nitro-2-picoline (30 mg, 0.17 mmol) was coupled with (S)-2-amino-butan-1-ol (32 mg, 0.21 mmol), and sodium acetate (28 mg, 0.34 mmol) in EtOH (2 mL) using the same procedure as described in Example-13. This gave 21 mg (53%) of (S)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-butan-1-ol as a yellow solid. $M/Z = 225$.

Example 13

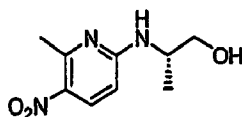
(DL)-3-(4-Chloro-phenyl)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

6-Chloro-3-nitro-2-picoline (50 mg, 0.29 mmol) was coupled with (DL)-2-amino-3-(4-chloro-phenyl)-propan-1-ol (103 mg, 0.55 mmol), in triethylamine (0.077 mL, 0.55 mmol) in DMSO (1 mL) using the same procedure as described in Example-1 but at 140 °C. This gave 23 mg (45%) of (DL)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-3-(4-chloro-phenyl)-propan-1-ol as a yellow solid. $M/Z = 321$.

Example 14

(S)-2-(6-Methyl-5-nitro-2-pyridin-2-ylamino)-propionic acid

6-Chloro-3-nitro-2-picoline (62 mg, 0.36 mmol) was coupled with L-alanine (80 mg, 0.90 mmol) and sodium acetate (78 mg, 0.95 mmol) in DMSO 1 mL. The reaction was heated to 140 °C for 600 seconds in a microwave oven (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The crude mixture was treated with a saturated aqueous solution of NH_4Cl . The reaction mixture was acidified to pH 4 (HCl , 1M). The crude reaction mixture was extracted with EtOAc, and the combined organic layers were washed with water and brine. Purification on silica using a mobile phase CH_2Cl_2 -MeOH-HOAc gave 60 mg (74%) of (S)-2-(6-methyl-5-nitro-2-pyridin-2-ylamino)-propionic acid as a yellow solid. $M/Z = 225$.

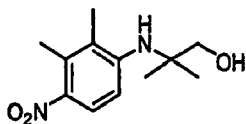
Example 15

(S)-2-(6-Methyl-5-nitro-2-pyridin-2-ylamino)-propan-1-ol

(S)-2-(6-Methyl-5-nitro-2-pyridin-2-ylamino)-propionic acid (60 mg, 0.27 mmol) was added to a nitrogen-purged flask with LiAlH_4 (27 mg, 0.71 mmol). The reaction mixture was refluxed for 2 h and then allowed to reach room temperature and then quenched by

sequentially adding H₂O (1 mL), NaOH (1M, 1 mL) and H₂O (1 mL). The slurry was centrifuged and the precipitated aluminum salts were washed with dichloromethane. The combined filtrates were evaporated and purification of the residue on a silica column with heptane- EtOAc (3:2) gave 13 mg (22%) of (S)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol as a yellow solid. M/Z = 211.

Example 16



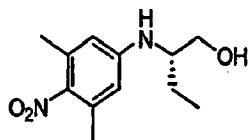
2-(2,3-Dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol

Fuming nitric acid (1.4 g, 20.3 mmol) was cooled to 0°C and acetic anhydride (2.89 g, 28.4 mmol) was added. This solution was added to a cold (0°C) solution of 3-fluoro-1,2-dimethylbenzene (1.0 g, 8.1 mmol) in acetic anhydride (4 ml) over 10 min. The reaction mixture was stirred for 25 min, poured slowly over ice and the water solution extracted with EtOAc (x 3). The collected organic phase was washed with diluted saturated aqueous solution of NaHCO₃ followed by brine before evaporation to dryness. The residue was flash purified on a silica gel column using hexane as a mobile phase to give 2,3-dimethyl-4-fluoro-1-nitro-benzene 0.74 g (54%) as a yellow oil which crystallised upon standing.

The fluoride (0.576 g, 3.4 mmol) was mixed with 2-amino-2-methylpropanol (0.61 g, 6.8 mmol) in a tube, and the tube was sealed before immersing it into an oil bath and heating at 160°C for 5 days. TLC (Hexane) showed remaining starting material. The reaction mixture was cooled and diluted with EtOAc before purification by flash silica gel chromatography (dry application; 6:4 hexane and EtOAc) to give 0.34 g (59% recovery) of the starting material 2,3-dimethyl-4-fluoro-1-nitro-benzene and 0.20 g (61% based on

recovered starting material) of the 2-(2,3-dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol. $M/Z = 238$.

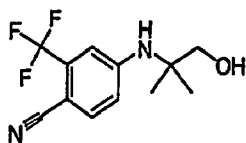
Example 17



(S)-2-(3,5-Dimethyl-4-nitro-phenylamino)-butan-1-ol

(S)-2-Amino-butan-1-ol (41 mg, 0.461 mmol) was dissolved in DMSO (800 μ L) and DIPEA (80 μ L, 0.461 mmol) added. 4-Fluoro-2-trifluoromethyl-benzonitrile (60mg, 0.354 mmol) was added and the reaction mixture was heated to 160 °C for 900 seconds in a microwave oven (Parameters: High absorbance, Fixed Holding time, pre-stirring 25 sec). The reaction mixture was then diluted with EtOAc and washed with an aqueous solution of NH_4Cl . The organic phase was then dried and evaporated *in vacuo*. The crude product was purified on silica column with 3:1 n-heptane:EtOAc as the mobile phase. This provided 22 mg (26 %) of (S)-2-(3,5-dimethyl-4-nitro-phenylamino)-butan-1-ol. $M/Z = 238$

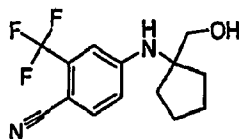
Example 18



4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-benzonitrile

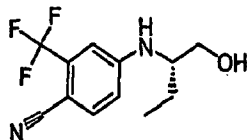
2-Amino-2-methyl-propan-1-ol (25 mg, 0.275 mmol) was dissolved in 0.7 mL DMSO and DIPEA (36 mg, 0.275 mmol) was added. 4-fluoro-2-trifluoromethyl-benzonitrile (40 mg, 0.212 mmol) was then added and the reaction was heated to 140 °C for 1100 seconds in a microwave oven (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The reaction was then diluted with 10 mL EtOAc, washed with an aqueous solution of NH₄Cl, dried with anhydrous MgSO₄, filtered and then the organic phase was evaporated *in vacuo*. The crude product was purified on silica column with 3:1 n-heptane:EtOAc as the mobile phase. Upon dissolving the crude product in the mobile phase, an insoluble precipitate was collected. On analysis this showed to be mainly pure product. All insoluble precipitate was dissolved in acetone, celite™ was added, whereafter the acetone was evaporated. The celite was then applied to a silica column with 2:1 n-heptane:EtOAc as the mobile phase to give 34 mg (62%) of 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-benzonitrile as beige crystals. *M/Z* = 258.

Example 19

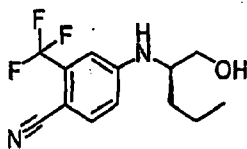


4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile

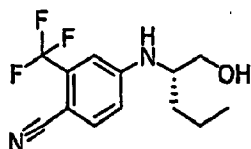
4-Fluoro-2-trifluoromethyl-benzonitrile (40 mg, 0.212 mmol) was coupled with (1-amino-cyclopentyl)-methanol (32 mg, 0.275 mmol), and DIPEA (36 mg, 0.275 mmol) in DMSO 0.7 mL using the same procedure as described in Example-8. This gave 23 mg (38%) of 4-(1-hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile as white powder. *M/Z* = 284.

Example 20**(S)-4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile**

4-Fluoro-2-trifluoromethyl-benzonitrile (40 mg, 0.212 mmol) was coupled with (S)-2-amino-butan-1-ol (25 mg, 0.275 mmol), DIPEA (36 mg, 0.275 mmol), in 0.7 mL DMSO using the same procedure as described in Example-8. This gave 17 mg (31%) of (S)-4-(1-hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile as white crystals. $M/Z = 258$.

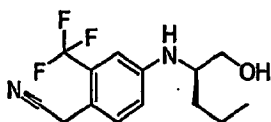
Example 21**(R)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile**

4-Fluoro-2-trifluoromethyl-benzonitrile (40 mg, 0.21 mmol), (R)-2-Amino-pentan-1-ol (32 mg, 0.27 mmol) and DIPEA (47 μ L, 0.27 mmol) was dissolved in DMSO (1 mL) and heated to 180 °C for 900 seconds in a microwave oven (Parameters: Fixed Holding time, High absorbance, pre-stirring 25 sec.). The crude product was diluted with CH_2CH_2 and washed with an aqueous solution of NH_4Cl . The organic phase was separated, dried and evaporated in vacuo. The crude product was purified on a silica column with 3:1 n-heptane: EtOAc as the mobile phase. This gave 39 mg (68%) of (R)-4-(1-hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile. $M/Z = 272$.

Example 22

(S)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile

4-Fluoro-2-trifluoromethyl-benzonitrile (40 mg, 0.21 mmol) was coupled with (S)-2-Amino-pentan-1-ol (32 mg, 0.27 mmol), DIPEA (47 μ L, 0.27 mmol) in DMSO 1.0 mL, using the same procedure as described in Example-21. This gave 24 mg (42%) of (S)-4-(1-hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile. $M/Z = 272$

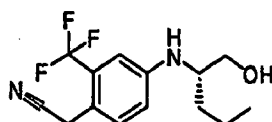
Example 23

[4-(R)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile

(4-Fluoro-2-trifluoromethyl-phenyl)-acetonitrile (100 mg, 0.492 mmol) was dissolved in DMSO (3.5 mL) and (R)-(-)-2-Amino-1-pentanol (66 mg, 0.634 mmol) and pyridine (52 μ L, 0.634 mmol) was added. The reaction was heated in microwave to 170 $^{\circ}$ C for 900 sec (Parameters: 30 seconds pre-stirring, holding time on, normal absorption). The mixture was diluted with EtOAc and washed with aqueous solution of NH_4Ac . The water phase was washed with EtOAc and the organic phases were pooled, dried with MgSO_4 , filtered

and evaporated *in vacuo*. The crude product was purified on a silica column with 5:1 *n*-heptane: EtOAc as the mobile phase. This gave 2.1 mg (1.5 %) of [4-(R)-1-hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile. $M/Z = 286$

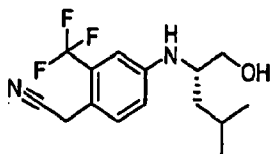
Example 24



[4-(S)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile

(4-Fluoro-2-trifluoromethyl-phenyl)-acetonitrile (100 mg, 0.492 mmol) was coupled with (S)-(+)-2-Amino-1-pentanol (66 mg, 0.634 mmol), Pyridine (52 μ L, 0.634 mmol), in DMSO (3.5 mL) using the same procedure as described in Example-23. This gave 2.2 mg (1.6 %) of [4-(S)-1-hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile. $M/Z = 286$

Example 25

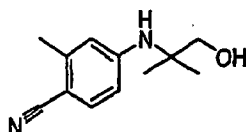


[4-(S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile

(4-Fluoro-2-trifluoromethyl-phenyl)-acetonitrile (119 mg, 0.584 mmol) was coupled with L-Leucinol (89 mg, 0.759 mmol), Pyridine (62 μ L, 0.759 mmol), DMSO (3.2 mL) using

the same procedure as described in Example-23. This gave 2.6 mg (1.5 %) of [4-((S)-1-hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile. M/Z = 300

Example 26



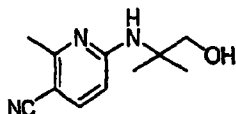
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile

The 2-methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol (360 mg, 1.6 mmol) was dissolved in ethanol (26 ml) and $\text{Na}_2\text{S}_2\text{O}_4$ (2.23 g, 12.8 mmol) was added and the solution heated at 80°C overnight. The solvent was evaporated and the remaining solid was partitioned between 10% aqueous solution NaHCO_3 and EtOAc. The water phase (pH = neutral) was extracted with EtOAc (x 3), the collected organic phase washed with brine and dried (MgSO_4). The 2-(4-amino-3-methyl-phenylamino)-2-methyl-propan-1-ol was used in the next step without further purification. (The amine oxidises on the TLC plate; brown spots upon standing.)

Sodium nitrite (NaNO_2) (190 mg, 2.75 mmol) in water (2.5 ml) was added to a solution of amine (500 mg, 2.5 mmol conc. HCl /ice (2.5 ml/2.5 g) during 5 min. followed by neutralisation by addition of solid CaCO_3 . KCN (391 mg, 6 mmol) and CuCN (269 mg, 3.0 mmol) in water (1 ml) was heated at 60°C (oil bath) and the cold, neutral diazonium salt solution was added drop wise over 15 min. Gas evolution was observed and the resulting suspension turned bright and strong orange. The reaction mixture was heated at 110°C for 30 min, cooled, diluted with water and EtOAc and filtered through celite. The water phase was extracted with EtOAc and the collected organic phase washed with brine and dried (MgSO_4). The crude product (491 mg) was purified by flash chromatography

(Hexane; Hex/EtOAc; 7:3 → 1:1) giving the reduced compound 2-methyl-2-(3-hydroxy-phenylamino)-propan-1-ol (93 mg) and 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile (108 mg, 21%) as a pale yellow solid. $M/Z = 204$.

Example 27



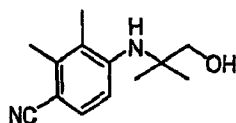
6-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-nicotinonitrile

2-Methyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol (1.08 g, 4.8 mmol) was dissolved in 75% aqueous ethanol and $\text{Na}_2\text{S}_2\text{O}_4$ (3.9 g, 24 mmol) was added in portions. The reaction mixture was heated at 60°C for 30 min when TLC (10% MeOH in DCM) showed full conversion. The heat was turned off, the reaction mixture stirred overnight at ambient temperature and evaporated to dryness. To this residue was added NaHCO_3 (5% aq.) and EtOAc, the phases separated and the water phase (pH 7-8) extracted extensively with EtOAc. (The product is very water-soluble and it is probably better to do a continuous extraction with EtOAc to get a higher yield). The collected organic phase was washed with brine before drying (MgSO_4). Upon standing, the colour of the organic solution turned from yellow to orange. Filtration and evaporation yielded 0.648 g (69%) of amine as a red oil.

NaNO_2 (0.25 g, 3.65 mmol) in water (3 ml) was added to a solution of amine 6 (0.648 g, 3.3 mmol) in ice/conc. HCl (3.5 g/3.5 ml) during 5 min. followed by neutralisation by addition of solid CaCO_3 . KCN (0.52 g, 7.96 mmol) and CuCN (0.36 g, 3.98 mmol) in water (3 ml) was heated at 60°C (oil bath) and the cold, neutral diazoniumsalt solution was added drop wise over 15 min. Gas evolution was observed and the resulting

suspension turned bright and strong orange. The reaction mixture was heated at 110°C for 30 min, cooled, diluted with water and EtOAc and filtered through celite. The water phase was extracted with EtOAc and the collected organic phase was washed with brine and dried (MgSO₄). The crude product (0.248 g) was purified by flash chromatography (Hexane → Hex :EtOAc 3:7) yielding 34 mg of 2-methyl-2-(6-methyl-pyridin-2-ylamino)-propan-1-ol and 11 mg of 6-(2-hydroxy-1,1-dimethyl-ethylamino)-2-methyl-nicotinonitrile. M/Z = 205.

Example 28



4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile

The nitro compound 18 (0.20 g, 0.84 mmol) was dissolved in EtOH (20 ml), Na₂S₂O₄ (1.1 g, 6.71 mmol) was added and the reaction mixture heated at 80°C overnight. The cold reaction mixture was filtered through celite, washed well with EtOAc and the filtrate evaporated to dryness. The crude 2-(4-amino-2,3-dimethyl-phenylamino)-2-methyl-propan-1-ol (0.292 g), pure by ¹H-NMR, was used as such in the next reactions.

The reaction was performed using the same procedure as described in Example-21 using 2-(4-amino-2,3-dimethyl-phenylamino)-2-methyl-propan-1-ol (0.175 g, 0.84 mmol) in conc. HCl/ice water (1 ml/5 ml), NaNO₂ (64 mg, 0.92 mmol) in water (1 ml), KCN (130 mg, 2 mmol) and CuCN (90 mg, 1 mmol) in water (1 ml). The crude product (341 mg) was purified by flash chromatography (Hexane; Hex 7/EtOAc 3) giving reduced compound 2-(2,3-dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol and 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile. All the fractions containing impure nitrile were collected and crystallised from hexane/EtOAc to give 25

mg (13%) of pure 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile.
M/Z = 218.

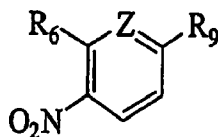
Procedure for Library synthesis (Examples 29-86).

The following is the general procedure for library synthesis for the examples of 29-88.
The compounds are shown in table 2.

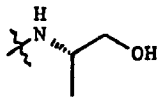
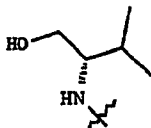
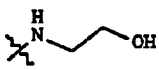
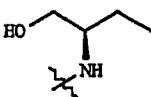
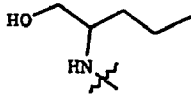
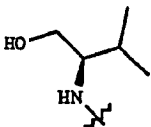
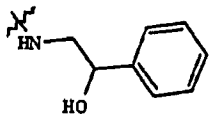
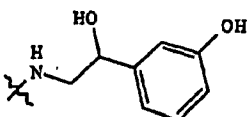
Smith-vials for the microwave oven were charged with 0.1 mmol either of the starting materials; 5-fluoro-2-nitro toluene, 5-fluoro-2-nitrobenzotrifluoride, 6-fluoro-2-methyl-3-nitro-pyridine.

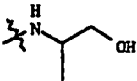
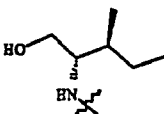
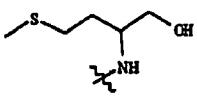
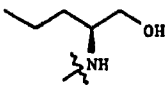
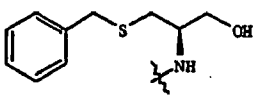
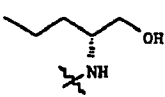
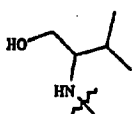
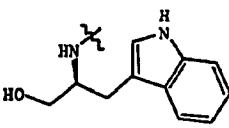
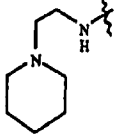
To each vial was added 0.5 ml DMSO, 20 μ L triethylamine (1.4 equivalents), and 1.4 equivalents of the diverse amino alcohols. The vials were run 1100s in 140°C in a microwave oven. After synthesis the products were analysed by LC-MS. The DMSO solutions were transferred to test tubes, and evaporated onto silica gel under reduced pressure. The silica gel from the tubes was placed on SPE SI columns, and a frit was placed on top. The products were purified with a gradient solution of heptane/EtOAc. The fractions were pooled and solvent was evaporated. Compounds which were more than 90% pure were tested in an *in vitro* assay which is described below. Purity was determined by analytic HPLC.

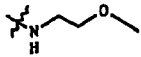
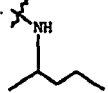
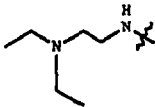

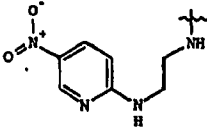
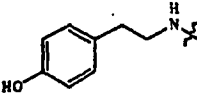
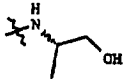
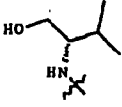
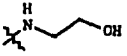
The scaffold used for the construction of the library is according to Formula II. The

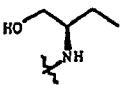
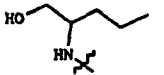
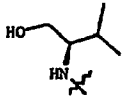
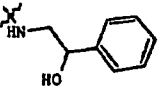
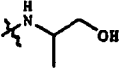
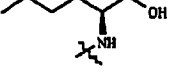
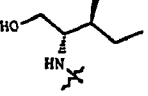
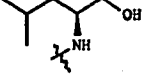
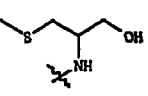


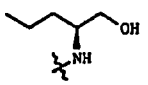
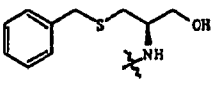
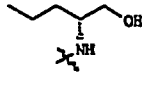
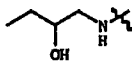
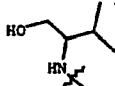
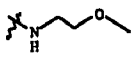


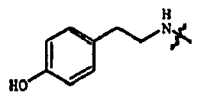
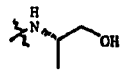
Formula II

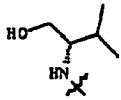
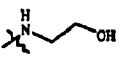
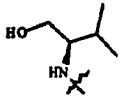
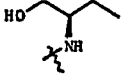
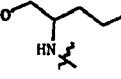
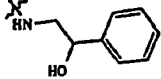
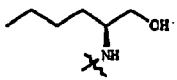
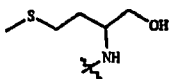
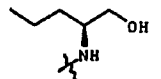
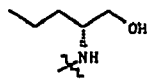
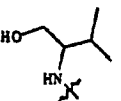
Example	R9	R6	Z	Yield (%)	MS (-Q1)
29		CF ₃	CH	46	262.9
30		CF ₃	CH	55	290.8
31		CF ₃	CH	24	249.1
32		CF ₃	CH	62	276.7
33		CF ₃	CH	65	290.8
34		CF ₃	CH	23	290.8
35		CF ₃	CH	93	325.3
36		CF ₃	CH	78	341.2

Example	R9	R6	Z	Yield (%)	MS (-Q1)
37		CF ₃	CH	82	262.9
38		CF ₃	CH	95	305.2
39		CF ₃	CH	98	323.2
40		CF ₃	CH	98	290.8
41		CF ₃	CH	89	385
42		CF ₃	CH	92	290.8
43		CF ₃	CH	95	290.8
44		CF ₃	CH	100	378.1
45		CF ₃	CH	84	316

Example	R9	R6	Z	Yield (%)	MS (-Q1)
46		CF ₃	CH	90	262.9
47		CF ₃	CH	106	275.2
48		CF ₃	CH	75	304.3
49		CF ₃	CH	69	275.2
50		CF ₃	CH	76	370
51		CF ₃	CH	89	325.3
52		CH ₃	N	53	238.0
53		CH ₃	N	53	238.0
54		CH ₃	N	30	195.7

Example	R9	R6	Z	Yield (%)	MS (-Q1)
55		CH ₃	N	60	223.9
56		CH ₃	N	63	238.0
57		CH ₃	N	22	238.0
58		CH ₃	N	88	272.2
59		CH ₃	N	65	209.8
60		CH ₃	N	60	252.1
61		CH ₃	N	79	252.1
62		CH ₃	N	89	252.1
63		CH ₃	N	74	270.4

Example	R9	R6	Z	Yield (%)	MS (-QI)
64		CH ₃	N	84	238.0
65		CH ₃	N	78	332.2
66		CH ₃	N	88	238.0
67		CH ₃	N	80	224.2
68		CH ₃	N	75	238.0
69		CH ₃	N	72	209.8
70		CH ₃	N	58	223.1
71		CH ₃	N	52	222.1
72		CH ₃	N	90	272.2
73		CH ₃	C	44.0	208.9

Example	R9	R6	Z	Yield (%)	MS (-Q1)
74		CH ₃	CH	55.0	237.1
75		CH ₃	CH	66.0	195.1
76		CH ₃	CH	31.0	237.1
77		CH ₃	CH	30.0	223
78		CH ₃	CH	32.0	237.1
79		CH ₃	CH	27	271.3
80		CH ₃	CH	25	250.9
81		CH ₃	CH	27	269.2
82		CH ₃	CH	24	237.1
83		CH ₃	CH	24	237.1
84		CH ₃	CH	24	237.1

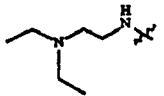
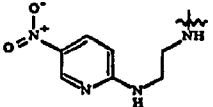
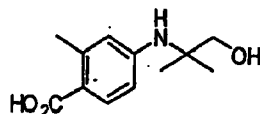
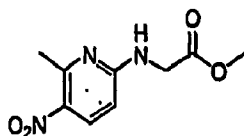
Example	R9	R6	Z	Yield (%)	MS (-Q1)
85		CH ₃	CH	25	250
86		CH ₃	CH	33	316

Table 2

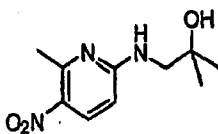
Example 874-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzoic acid

A suspension of 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile (70 mg, 0.34 mmol) and NaOH (0.14 g, 3.4 mmol) in water/MeOH (5 ml/8 ml) was refluxed for 4 days. The reaction mixture was diluted with water, pH adjusted to approx. 3 with 50% aq. HCl. The precipitated solid was filtered off and collected, the water phase was extracted with EtOAc (x 3), washed with brine and dried (MgSO₄). The crude product was purified on a silica column with 1:1 n-heptane: EtOAc as mobile phase. This gave 39 mg (51%) of the 4-(2-hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzoic acid as a brownish foam. M/Z 223.

Example-88

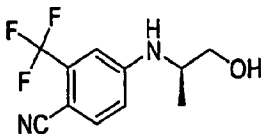
(6-Methyl-5-nitro-2-pyridin-2-ylamino)-butionic methyl ester

6-chloro-3-nitro-2-picoline (600 mg, 3.5 mmol) was coupled with glycine methyl ester hydrochloride (880 mg, 7 mmol), triethylamine (1.5 ml, 10.5 mmol) in DMSO 3 mL at 140 °C for 30 min in microwave (Parameters: high absorbance, fixed holding time, pre-stirring 25 seconds). The crude mixture was treated with a saturated aqueous solution of NH_4Cl . The aqueous solution of was extracted with EtOAc, washed with water and brine. The crude product was purified on a silica column with CH_2Cl_2 -MeOH as mobile phase. This gave 39 mg (51%) of 580 mg (74%) of (6-methyl-5-nitro-2-pyridin-2-ylamino)-butionic methyl ester as a yellow solid. $M/Z = 225$.

Example-89

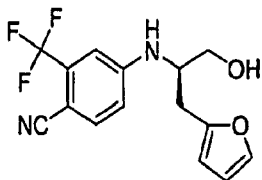
2-Methyl-N-(6-methyl-5-nitro-pyridin-2-yl amino)-propan-2-ol

2-(6-Methyl-5-nitro-pyridin-2-ylamino)-butionic methyl ester (30 mg, 0.13 mmol) was dissolved in THF (3 mL) and added to a nitrogen-purged flask containing methyl magnesium chloride (MeMgCl) (0.08 mL, 0.027 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and then refluxed for 5 h. The reaction was quenched by adding saturated NH_4Cl . The reaction mixture was extracted with EtOAc and washed with H_2O and brine. The crude product was purified by HPLC. This gave 1.5 mg (5%) of 2-methyl-N-(6-methyl-5-nitro-pyridin-2-yl amino)-propan-2-ol as yellow oil. $M/Z = 225$.

Example-90

4-((R)-2-Hydroxy-1-methyl-ethylamino)-2-trifluoromethyl-benzonitrile

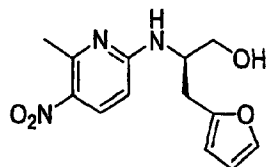
D-Alanine (36 mg, 0.40 mmol) was dissolved in THF (dry, 1 ml) and the vials were purged with N₂ for 5 min. BF₃-Et₂O (0.050 ml, 0.40 mmol) was added with syringe and the mixture was heated at 70°C for 1.5 h. BH₃-SMe₂ (0.22 ml, 0.44 mmol, 2M solution) was added carefully during vigorous stirring (an exotherm was formed approx half way) (a evolution of gas was noticed). The reactions was purged with N₂ and then heated at 70°C over night (17h). The reaction was allowed to cool to room temp. The excess borane was quenched by addition of 1 ml of a 1:1 mixture of THF: H₂O, followed by 1 ml of NaOH (5M). The two phase system was heated at 70°C in 4h. The flask was purged with N₂ to blow off the THF. CH₂Cl₂ (2 ml) was added and the two phase system was transformed to a Phase separator. Additional CH₂Cl₂ (2 ml) was added and the combined organic phases were evaporated. The crude (21 mg) was then dissolved in DMSO and the reaction was continued as in example 1. 4-Fluoro-2-trifluoromethyl-benzonitrile (19 mg, 0.1 mmol) was coupled with the formed (R)-2-amino-propan-1-ol. DIPEA (0.021 ml, 0.12 mmol), in 1 mL DMSO using the same procedure as described in Example-1. Purification on preparative HPLC gave 4 mg (16 %) of 4-((R)-2-Hydroxy-1-methyl-ethylamino)-2-trifluoromethyl-benzonitrile as a white solid. M/Z= 244.

Example-91

4-((R)-1-Furan-2-ylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

(R)-2-Amino-3-furan-2-yl-propionic acid (40 mg, 0.25 mmol) was reduced using the same procedure as described in Example-90. The crude was coupled with 4-Fluoro-2-trifluoromethyl-benzonitrile (19 mg, 0.1 mmol) and DIPEA (0.05 ml, 0.2 mmol) as in example 1 and gave 4-((R)-1-furan-2-ylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile 11 mg (29%), after purification on HPLC, as a white solid. $M/Z = 310$.

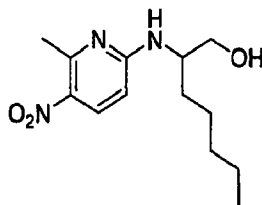
Example-92



(R)-3-Furan-2-yl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

(R)-2-Amino-3-furan-2-yl-propionic acid (40 mg, 0.25 mmol) was reduced using the same procedure as described in Example-90. The crude was coupled with 6-chloro-3-nitro-2-picoline (17 mg, 0.1 mmol) and DIPEA (0.05 ml, 0.2 mmol) as in example 1 and gave, after purification on HPLC, 9 mg (33%) of (R)-3-Furan-2-yl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol, as a white solid. $M/Z = 277$.

Example-93

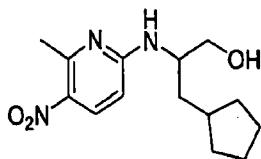


2-(6-Methyl-5-nitro-pyridin-2-ylamino)-heptan-1-ol

2-Amino-heptanoic acid (33 mg, 0.25 mmol) was reduced using the same procedure as described in Example-90. The crude was coupled with 6-chloro-3-nitro-2-picoline (17 mg, 0.1 mmol) and DIPEA (0.05 ml, 0.2 mmol) as in Example 1 and gave after

purification on HPLC, 3 mg (11 %) 2-(6-methyl-5-nitro-pyridin-2-ylamino)-heptan-1-ol, as an oil. $M/Z = 267$

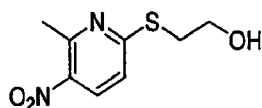
Example-94



3-Cyclopentyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

2-Amino-3-cyclopentyl-propionic acid (36 mg, 0.25 mmol) was reduced using the same procedure as described in Example-90. The crude was coupled with 6-chloro-3-nitro-2-picoline (17 mg, 0.1 mmol) and DIPEA (0.05 ml, 0.2 mmol) as in Example 1 and gave, after purification on HPLC, 4 mg (14 %) 3-Cyclopentyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol, as a yellow solid. $M/Z = 279$.

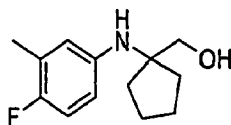
Example-95



2-(6-Methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol

6-Chloro-3-nitro-2-picoline (17 mg, 0.1 mmol) was coupled with 2-Mercapto-ethanol (0.014 ml, 0.2 mmol), DIPEA (25 mg, 0.2 mmol) in DMSO 0.8 mL, using the same procedure as described in Example-1. This gave 5 mg (23%) of 2-(6-Methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol as a yellow oil. $M/Z = 214$.

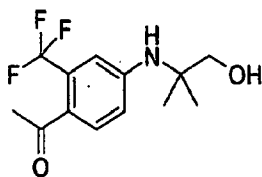
Example 96



[1-(4-Fluoro-3-methyl-phenylamino)-cyclopentyl]-methanol

4-Fluoro-2-methyl phenol (0.24 mmol) was solved in 800 μL DMSO. (1-Amino-cyclopentyl)-methanol (0.29 mmol) was added and then Diisopropyl-ethyl amine (DIPEA) (0.29 mmol). Reaction was heated to 180 $^{\circ}\text{C}$ in microwave for 15 min (Parameters: Normal absorption, hold time on, pre-stirring 20 sec). Starting material was remaining so reaction was heated to 220 $^{\circ}\text{C}$ for additional 15 min. Several products obtained. Crude mixture was diluted in CH_2Cl_2 and washed several times with NH_4Cl (aq) and phases were separated on SPE Phase Separator. Organic phase was evaporated *in vacuo* and crude product mixture was then purified on silica column with 5:1 n-heptane:EtOAc as mobile phase. This gave 2.3 mg (4 %) of [1-(4-fluoro-3-methyl-phenylamino)-cyclopentyl]-methanol. $M/Z = 221$

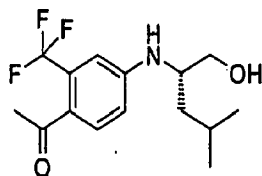
Example 97



1-[4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-phenyl]-ethanone

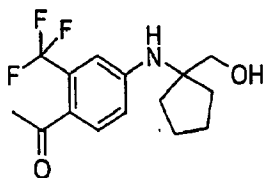
1-(4-Fluoro-2-trifluoromethyl-phenyl)-ethanone (40mg, 0.194 mmol) was solved in 800 μL DMSO. 2-Amino-2-methyl-propan-1-ol (23mg, 0.252 mmol) was added and then DIPEA (44 μL , 0.252 mmol). Reaction mixture was heated to 180 $^{\circ}\text{C}$ in microwave for 15 min (Parameters: Normal absorption, hold time on, pre-stirring 25 sec). Majority of starting material still left so reheated to 210 $^{\circ}\text{C}$ for 15 min. Several products obtained. Crude mixture was diluted in CH_2Cl_2 and washed several times with NH_4Cl (aq) and phases were separated on SPE Phase Separator. Organic phase was evaporated *in vacuo* and crude product mixture was then purified on silica column with 10:1 n-heptane:EtOAc as mobile phase. This gave 3 mg (6%) of 1-[4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-phenyl]-ethanone as minor product. $M/Z = 275$.

Example 98



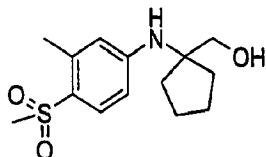
1-[4-((S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-ethanone

1-(4-Fluoro-2-trifluoromethyl-phenyl)-ethanone (40 mg, 0.194 mmol) was coupled with (S)-2-Amino-4-methyl-pentan-1-ol (30mg, 0.252 mmol), DIPEA (44 μL , 0.252 mmol) in DMSO 800 μL using the same procedure as described in Example-97. This gave 15 mg (25 %) of 1-[4-((S)-1-hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-ethanone. $M/Z = 303$

Example 99

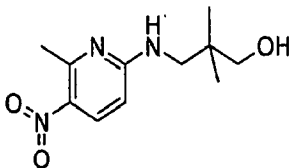
1-[4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-phenyl]-ethanone

1-(4-Fluoro-2-trifluoromethyl-phenyl)-ethanone (40 mg, 0.194 mmol) was coupled with (1-Amino-cyclopentyl)-methanol (29 mg, 0.252 mmol), DIPEA (44 μ L, 0.252 mmol), in DMSO 800 μ L using the same procedure as described in Example-97. This gave 5 mg (9 %) of 1-[4-(1-hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-phenyl]-ethanone. M/Z = 301.

Example 100

[1-(4-Methanesulfonyl-3-methyl-phenylamino)-cyclopentyl]-methanol

4-Fluoro-1-methanesulfonyl-2-methyl-benzene (40 mg, 0.213 mmol) was solved in 800 μ L DMSO. (1-Amino-cyclopentyl)-methanol (32 mg, 0.276 mmol) was added and DIPEA (48 μ L, 0.276 mmol). Reaction mixture was heated to 180 $^{\circ}$ C in microwave for 15 min (Parameters: Normal absorption, hold time on, pre-stirring 30 sec). Crude mixture was diluted in CH_2Cl_2 and washed several times with NH_4Cl (aq) and phases were separated on SPE Phase Separator. Organic phase was evaporated *in vacuo* and crude product mixture was then purified on silica column with 7:1 n-heptane:EtOAc as mobile phase. This gave 1.4 mg (2 %) of [1-(4-methanesulfonyl-3-methyl-phenylamino)-cyclopentyl]-methanol. M/Z = 283

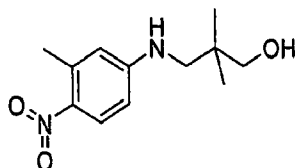
Example 101

2,2-Dimethyl-3-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

6-Chloro-2-methyl-3-nitro-pyridine (40 mg, 0.232 mmol) was solved in 900 μ L DMSO. 3-Amino-2,2-dimethyl-propan-1-ol (31 mg, 0.301 mmol) and DIPEA (52 μ L, 0.301 mmol) was added and heated to 180 $^{\circ}$ C in microwave for 15 min parameters: Normal

absorption, hold time on, pre-stirring 30 sec). Crude mixture was diluted in CH_2Cl_2 and washed several times with NH_4Cl (aq) and phases were separated on SPE Phase Separator. Organic phase was evaporated *in vacuo* and crude product mixture was then purified on silica column with 7:1 n-heptane:EtOAc as mobile phase. This gave 15 mg (27 %) of 2,2-dimethyl-3-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol. $M/Z = 239$

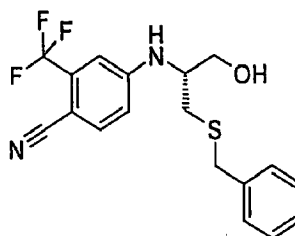
Example 102



2, 2-Dimethyl-3-(3-methyl-4-nitro-phenylamino)-propan-1-ol

4-Fluoro-2-methyl-1-nitro-benzene (40 mg, 0.258 mmol) was coupled with 3-Amino-2,2-dimethyl-propan-1-ol (35 mg, 0.335 mmol), DIPEA (58 μL , 0.335 mmol) in DMSO 900 μL using the same procedure as described in Example-101. This gave 4 mg (7 %) of 2, 2-dimethyl-3-(3-methyl-4-nitro-phenylamino)-propan-1-ol. $M/Z = 238$.

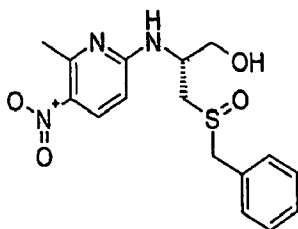
Example 103



4-((R)-1-Benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

4-Fluoro-2-trifluoromethyl-benzonitrile (60 mg, 0.32 mmol) was solved in 1000 μL DMSO. (R)-2-amino-3-benzylsulfanyl-propan-1-ol (81 mg, 0.41 mmol) was added and then diisopropyl-ethyl amine (DIPEA) (53 mg, 0.41 mmol). Reaction was heated to 180 $^{\circ}\text{C}$ in microwave for 15 min (Parameters: Normal absorption, hold time on, pre-stirring 20 sec). Crude mixture was diluted in CH_2Cl_2 and washed several times with NH_4Cl (aq) and phases were separated on SPE Phase Separator. Organic phase was evaporated *in vacuo* and crude product mixture was then purified on silica column with 3:1 n-heptane:EtOAc as mobile phase. This gave pure product 82 mg (71 %) of 4-((R)-1-benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile as transparent oil. $M/Z = 366$

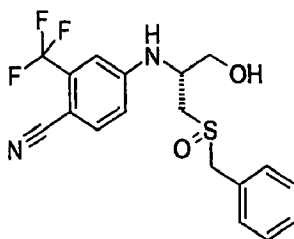
Example 104



(R)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenylmethanesulfinyl-propan-1-ol

CH_2Cl_2 (0.125 mL) was cooled to 0 °C and mCPBA (13 mg, 0.07 mmol) was solved in it. Stirred at 0 °C for 10 min then (R)-3-benzylsulfanyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol (20 mg, 0.06 mmol) was added. Stirred at 0 °C for 20 min. Cooling bath was removed and reaction was allowed to warm to room temperature and was then stirred overnight. The organic phase was washed with brine, phases were separated on SPE Phase Separator and organic phase was dried and evaporated *in vacuo*. Crude product gives precipitation on salvation in 3:1 n-Heptane:EtOAc. Precipitate was consisting of mainly product and was solved in acetonitrile and purified on silica column with EtOAc as mobilephase. This gave 8.2 mg (39 %) of (R)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenylmethanesulfinyl-propan-1-ol. $M/Z = 349$.

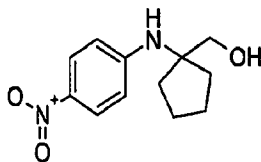
Example 105



4-((R)-2-Hydroxy-1-phenylmethanesulfinylmethyl-ethylamino)-2-trifluoromethyl-benzonitrile

4-((R)-1-Benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile (20 mg, 0.06 mmol) was reacted with mCPBA (11 mg, 0.07 mmol) in CH_2Cl_2 (0.125 mL) using the same procedure as described in Example-104. This gave 14.1 mg (67 %) of 4-((R)-2-Hydroxy-1-phenylmethanesulfinylmethyl-ethylamino)-2-trifluoromethyl-nicotinonitrile. $M/Z = 382$

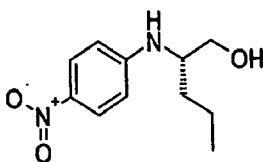
Example 106



[1-(4-Nitro-phenylamino)-cyclopentyl]-methanol

1-Fluoro-4-nitro-benzene (41 mg, 0.29 mmol) was solved in 1000 μ L DMSO. (1-amino-cyclopentyl)-methanol (44 mg, 0.38 mmol) was added and then diisopropyl-ethyl amine (DIPEA) (49 mg, 0.38 mmol). Reaction was heated to 170 $^{\circ}$ C in microwave for 15 min (Parameters: Normal absorption, hold time on, pre-stirring 30 sec). Crude mixture was diluted in EtOAc and washed several times with NH_4Cl (aq) and phases were separated. Organic phase was dried and then evaporated *in vacuo*. Crude product mixture was purified on silica column with 3:1 n-heptane:EtOAc as mobile phase. This gave 48 mg (70 %) of [1-(4-nitro-phenylamino)-cyclopentyl]-methanol. $M/Z = 236$.

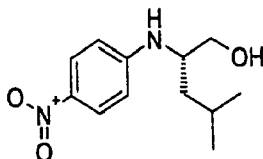
Example 107



(S)-2-(4-Nitro-phenylamino)-pentan-1-ol

1-Fluoro-4-nitro-benzene (41 mg, 0.29 mmol) was coupled with (S)-2-amino-pentan-1-ol (39 mg, 0.38 mmol), diisopropyl-ethyl amine (DIPEA) (49 mg, 0.38 mmol) in DMSO 1000 μ L using the same procedure as described in Example-106. This gave 53 mg (81 %) of (S)-2-(4-nitro-phenylamino)-pentan-1-ol. $M/Z = 224$

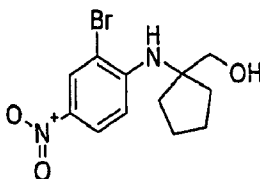
Example-108



(S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol

1-Fluoro-4-nitro-benzene (42 mg, 0.29 mmol) was coupled with (S)-2-amino-4-methyl-pentan-1-ol (50 mg, 0.38 mmol), diisopropyl-ethyl amine (DIPEA) (50 mg, 0.38 mmol) in DMSO 1000 μ L using the same procedure as described in Example-106. This gave 40 mg (57 %) of (S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol. $M/Z = 238$.

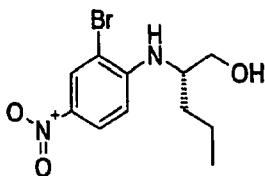
Example 109



[1-(2-Bromo-4-nitro-phenylamino)-cyclopentyl]-methanol

[1-(4-Nitro-phenylamino)-cyclopentyl]-methanol (10 mg, 0.042 mmol) was solved in a 1:1 mixture of CH_2Cl_2 : MeOH (2 mL). CaCO_3 (8.5 mg, 0.085 mmol) was added and the solution was stirred at roomtemp for 10 min. Benzyltrimethylammonium tribromide (36 mg, 0.093 mmol) was added and the reaction was stirred at roomtemp for 48 h. Crude reaction was diluted with CH_2Cl_2 and washed with $\text{NH}_4\text{Cl}_{(\text{aq})}$. Organic phase was collected, dried and evaporated *in vacuo*. Crude product was purified on silica column. This gave 11 mg (83 %) of [1-(2-bromo-4-nitro-phenylamino)-cyclopentyl]-methanol. $M/Z = 315$.

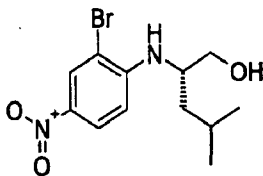
Example 110



(S)-2-(2-Bromo-4-nitro-phenylamino)-pentan-1-ol

(S)-2-(4-Nitro-phenylamino)-pentan-1-ol (29 mg, 0.13 mmol) was treated benzyltrimethylammonium tribromide (111 mg, 0.29 mmol) and CaCO_3 (26 mg, 0.26 mmol) in 1:1 mixture of CH_2Cl_2 : MeOH (2 mL) using the same procedure as described in Example-109. This gave 16 mg (41 %) of (S)-2-(2-Bromo-4-nitro-phenylamino)-pentan-1-ol. $M/Z = 303$.

Example 111



(S)-2-(2-Bromo-4-nitro-phenylamino)-4-methyl-pentan-1-ol

(S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol (29 mg, 0.13 mmol) was treated benzyltrimethylammonium tribromide (111 mg, 0.30 mmol) and CaCO_3 (26 mg, 0.27 mmol) in 1:1 mixture of CH_2Cl_2 :MeOH (2 mL) using the same procedure as described in Example-109. This gave 20 mg (47 %) of (S)-2-(2-Bromo-4-nitro-phenylamino)-4-methyl-pentan-1-ol. $M/Z = 317$.

All molecules were named by Autonom 2000, part of was IS/Draw 2.5

All naming done by was IS/Draw 2.5 with Autonom 2000

Example- 112

AR Competition Binding Assay

Recombinant human androgen receptor (hAR) was extracted from Sf9 insect cells with buffer containing 1 mM EDTA, 20 mM K_2HPO_4 , 8.7% glycerol, 20 mM Na_2MoO_4 and 12 mM MTG at 5×10^7 cells/ml. The cell debris was removed by centrifugation and the supernatant aliquoted and stored at $-70^\circ C$.

An aliquot of AR extract was thawed on ice prior to use and diluted to approximately 0.2 nM (1 to 30 dilution) in buffer (100 mM $K_nH_mPO_4$ pH 7.0, 1 mM EDTA, 8.7% glycerol, 20 mM Na_2MoO_4 and 1 mM DTT). The test ligands were diluted in DMSO as a dilution series of 10 concentrations in duplicate, with 1:5 dilution between each concentration.

Tritiated mibolerone (3H -Mib) was used as tracer compound and diluted to 1.6 nM in 1 mM EDTA, 20 mM Na_2MoO_4 , 8.7% glycerol and 1 mM DTT. To a 96-well polypropylene-plate 110 μ l/well of 1.6 nM 3H -Mib, 10 μ l/well test substance and 110 μ l/well diluted AR was added. The plates were covered and incubated at $+4^\circ C$ over night. The plates were harvested on filters to separate bound ligand from unbound ligand with a Tomtec Harvester. A prewet buffer containing 20 mM $K_n(PO_4)$ pH 7.6, 1 mM EDTA, v/v 0.5% polyethyleneimine was used to equilibrate the filter before filtering the samples and washing the filters with 20 mM $K_n(PO_4)$ pH 7.6, 1 mM EDTA 8 times. The filters were allowed to dry for 1 hour at $+65^\circ C$. A scintillating wax was melted upon the filter and the radioactivity retained on the filter was measured in a Wallac Microbeta scintillation counter.

The affinity to AR was evaluated by a non-linear four-parameter logistic model: $b = (b_{\max} - b_{\min}) / (1 + (IC_{50}/I)^S) + b_{\min}$, where b_{\max} = total concentration of binding sites, b_{\min} = non-specific binding, I = added concentration of binding inhibitor, IC_{50} = concentration of binding inhibitor at half-maximal binding and S = slope factor.

Table: Antagonist and partial antagonist and binding activity of androgen receptor modulator compounds.

AR Transactivation Assays

The agonist and antagonist properties of compounds were determined using a cell-based system expressing stably integrated androgen receptor and an androgen responsive reporter gene. CV-1 cells (kidney fibroblasts) stably expressing CMV-hAR and alkaline phosphatase (ALP) driven by an MMTV promoter containing an androgen response element were cultured in Dulbecco's Modified Eagle Medium (DMEM), low glucose supplemented with 10% fetal bovine serum, 1% L-glutamine, and 0.7% Hygromycin B. The stably integrated cells (ARAF) were trypsinized and resuspended in Opti-MEM 1 supplemented with 2% fetal bovine serum, 1% L-Glutamine, 50 µg/ml Gentamicin and 1% Pen/Strep. The cells were counted in a Birch chamber and diluted to a concentration of 100 000 cells /ml. The cells were then seeded out in 384 plates, 5000cells/well in 50µl seeding media and incubated overnight in 37 C, 5% CO₂.

The next day, the seeding medium was removed from the cells and 20 µl induction media (Opti-MEM 1 supplemented with 1% L- Glutamine, 50 µg/ml Gentamicin and 1% Pen/Strep) +/- 0.1 nM Mibolerone was added to the wells. 10µl of test compound diluted in induction media was then added to the wells. The cells were incubated 48 hr in 37 C, 5% CO₂.

After 48 hr 5µl of cell medium was added to white 384 plates with 100µl of ALP substrate buffer. The plates were incubated in 37 C for 20 minutes followed by incubation at room temperature for 10 minutes before each well was read in a µBETA machine. Agonist activity was calculated from the alkaline phosphatase activity induced

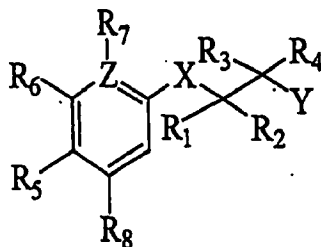
in the absence of Mibolerone and compared to standard activation curve generated by Mibolerone alone. Antagonist activity was calculated from the decrease in ALP activity in the presence of 0.1 nM Mibolerone. EC50 and IC50 values were calculated by using a non-linear four-parameter fit as described above.

Other assays to determine androgen receptor mediated activity of the test compounds include modulation of endogenous AR mediated transcription in cell culture systems; modulation of androgen responsive tissue effects in rodents; identification of receptor surface conformation changes; and binding specificity to AR versus other nuclear receptors.

	AR _{LT} IC50 (nM)	ARAF EC50 (nM)	ARAF %AGONIST	ARAF IC50 (nM)	ARAF % ANTAGONIST
Example-1	22.77	26.8	51.7	2.1	33.1
Example-5	38.06	81.7	29.3	7.2	61
Example-8	241.44	374.2	10.6	22.3	82.5
Example-19	130.38			22.4	95.6
Example-30	113.45	1069.9	7.3	68.3	88.7
Example-41	65.10			490.3	71.7
Example-42	485.50			493.3	92
Example-60	68.30	336.3	9.3	27.4	79.3
Example-61	89.30			68.3	87.4
Example-65	6.20	1867.3	7	78.0	89.2
Example-78	54.50	279.7	25	25.8	65.4
Example-86	443.40			350.7	100
Example-107	98.70			135.5	92.9
Example-110	170.30			240.7	86.2

CLAIMS

1. Use of a compound according to Formula I in the manufacture of a medicament for the treatment of a disease caused by a disturbance in the activity of the androgen receptor, wherein Formula I is defined as:



Formula I

in which;

R₁ and R₂ are the same or different and independently selected from the group consisting of; hydrogen, halogen, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkenoxy, C₁-C₁₀ alkynoxy, C₁-C₁₀ alkylthio, C₁-C₁₀ alkenylthio, C₁-C₁₀ alkynylthio, C₆-C₁₀ arylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarylthio, C₁-C₁₀ alkylarylulphone, C₁-C₁₀ alkylarylulphoxide, C₆-C₁₀ aryl, or C₃-C₂₀ heteroaryl, optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different; or R₁ and R₂ may together form a C₃-C₁₀ cycloalkyl group;

R₃ and R₄ are the same or different and independently selected from hydrogen, halogen, C₁-C₂₀ alkyl, C₃-C₇ cycloalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₄ alkoxy, C₁-C₄ alkenoxy, C₁-C₄ alkynoxy, C₁-C₄ alkylthio, C₁-C₄ alkenylthio, C₁-C₄ alkynylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarylthio, C₁-C₁₀ alkylarylulphone, C₁-C₁₀ alkylarylulphoxide, C₆-C₁₅ aryl, C₃-C₂₀ heteroaryl optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different; or can together form a keto group;

R₅ is chosen from the group consisting of; nitro, cyano, -CH₂CN, -COMe, acetic acid, halogen, sulphonic acid, -SO₂CH₃, aldehyde, carboxylic acid or ester, phosphonic acid or ester;

R_6 is chosen from the group consisting of; hydrogen, C_1 - C_3 alkyl, halogen, CN, CO_2H , CHF_2 , CH_2F or CF_3 ;

R_7 is chosen from the group consisting of; H, halogen or C_1 - C_3 alkyl;

R_8 is chosen from the group consisting of; hydrogen, C_1 - C_3 alkyl, halogen, CHF_2 , CH_2F or CF_3 ;

X is chosen from the group consisting of; -NH-, -O-, -S-, -SO-, - SO_2 -, -Se-, -Te- or -S-S-

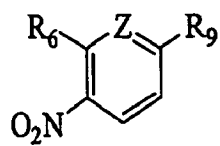
Y is chosen from the group consisting of; hydrogen, hydroxy, - CH_2OH , methoxy, NH_2 , unbranched, branched or cyclic C_1 - C_3 alkyl, unbranched, branched or cyclic - $NH(C_1C_3)$; unbranched, branched or cyclic $N(C_1-C_3)_2$, - $NH(C_6\text{aryl})$, - $N(C_6\text{aryl})_2$, - $NH(C_1C_{10}\text{heteroaryl})$, and - $N(C_5C_{10}\text{heteroaryl})_2$, $C_5C_{10}\text{heteroaryl}$ wherein any of said aryl or heteroaryl groups are optionally substituted with up to 3 groups of R^a which groups may be the same or different;

Z is chosen from the group consisting of; C, N, or O;

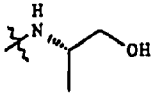
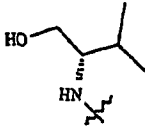
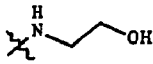
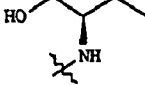
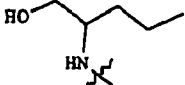
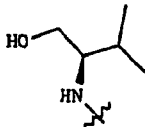
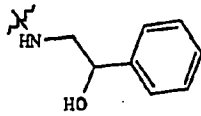
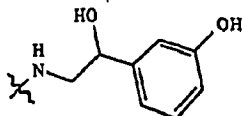
R^a represents a member selected from: hydrogen, halogen, -CN, OH, CO_2H , CHO, NO_2 , - NH_2 , - $NH(C_1C_4)$; $N(C_1C_4)_2$, - $NH(C_6\text{aryl})$, - $N(C_6\text{aryl})_2$, - $NH(C_5C_{10}\text{heteroaryl})$, and - $N(C_5C_{10}\text{heteroaryl})_2$; or a pharmaceutically acceptable salt thereof.

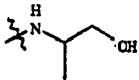
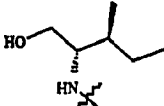
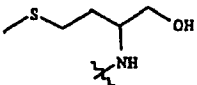
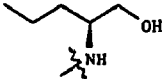
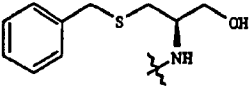
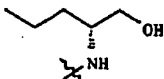
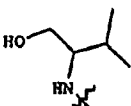
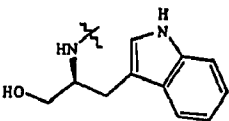
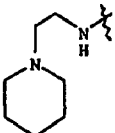
2. Use according to claim 1, wherein R_1 or/and R_2 are H, (S)-methyl, methyl, (R)-ethyl, (S)-ethyl, ethyl, (R)-propyl, (S)-propyl, propyl, (S)-butyl, (S)-1-methyl-propyl, (S)-2-methyl-propyl, (R)-isopropyl, (S)-isopropyl, isopropyl, cyclopentyl, $-(CH_2)_2SMe$, (R)- CH_2SCH_2Ph , (S)-benzyl, 4-chloro-benzyl, (S)-3-methyl-1-H-indole or (S)-phenyl;
3. Use according to either of the preceding claims wherein R_3 is chosen from the group consisting of; hydrogen, methyl, ethyl, phenyl, 3-hydroxy phenyl, 4-hydroxy phenyl, or forms a keto group together with R_4 .
4. Use according to any of the preceding claims wherein R_4 is H, methyl, or forms a keto group together with R_3 .
5. Use according to any of the preceding claims wherein R_5 is NO_2 , CN, CH_2CN or CO_2H ;
6. Use according to any of the preceding claims wherein R_6 is Me, or CF_3 ;
7. Use according to any of the preceding claims wherein R_7 is H or Me;
8. Use according to any of the preceding claims wherein R_8 is H or methyl;
9. Use according to any of the preceding claims wherein X is NH;
10. Use according to any of the preceding claims wherein Y is H, -OH, -OMe, -N $(CH_2CH_3)_2$, piperidine, or 4-nitro-2-ylamino;
11. Use according to any of the preceding claims wherein Z is CR_7 or N;
12. Use according to any of the preceding claims wherein the compound is chosen from the group consisting of;
 - 2-Methyl-2-(4-nitro-3-trifluoromethyl-phenylamino)-propan-1-ol;
 - [1-(4-Nitro-3-trifluoromethyl-phenylamino)-cyclopentyl]-methanol;
 - (S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-3-phenyl-propan-1-ol;



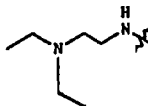

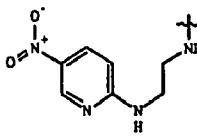
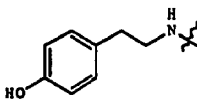
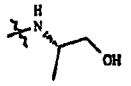
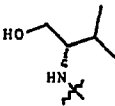
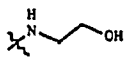
(S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-butan-1-ol;
2-Methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol;
[1-(3-Methyl-4-nitro-phenylamino)-cyclopentyl]-methanol;
(S)-2-(3-Methyl-4-nitro-phenylamino)-butan-1-ol;
2-Methyl-2-(6-methyl-5-nitro-pyridine-2-ylamino)-propan-1-ol;
[1-(6-Methyl-5-nitro-pyridine-2-ylamino)-cyclopentyl]-methanol;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-2-phenyl-ethanol;
(S)-2-(6-Methyl-5-nitro-pyridine-2-ylamino)-3-phenyl-propan-1-ol;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-butan-1-ol;
(DL)-3-(4-Chloro-phenyl)-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol;
(S)-2-(6-Methyl-5-nitro-2-pyridin-2-ylamino)-propionic acid;
(S)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol;
2-(2,3-Dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol;
(S)-2-(3,5-Dimethyl-4-nitro-phenylamino)-butan-1-ol;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-benzonitrile;
4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
(S)-4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
(R)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;
(S)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;
[4-((S)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
[4-((R)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
[4-((S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile;
6-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-nicotinonitrile;
4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile;
and compounds having the formula:

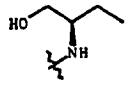
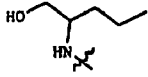
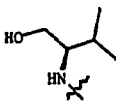
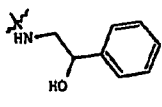
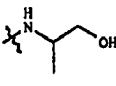
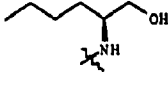
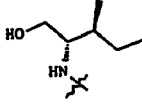
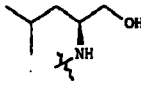
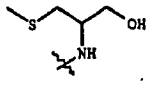


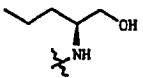
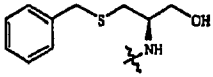
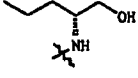
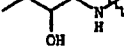
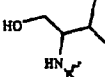



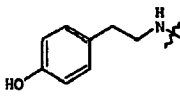
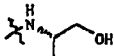
in which R_9 , R_6 and Z are as defined in the following table:

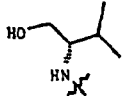
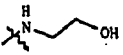
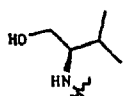
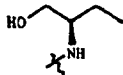
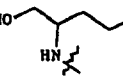
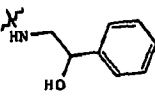
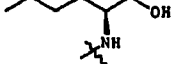
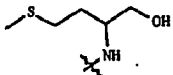
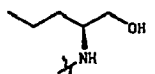
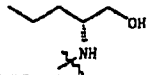
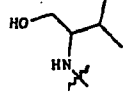
R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH

R9	R6	Z		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		

R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	CH

R9	R6	Z		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		
	CH ₃	CH		

[illegible]

4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzoic acid;

(6-Methyl-5-nitro-2-pyridin-2-ylamino)-butionic methyl ester,

2-Methyl-N-(6-methyl-5-nitro-pyridin-2-yl amino)-propan-2-ol:

4-((R)-2-Hydroxy-1-methyl-ethylamino)-2-trifluoromethyl-benzonitrile

4-((R)-1-Furan-2-ylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

(R)-3-Furan-2-yl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

2-(6-Methyl-5-nitro-pyridin-2-ylamino)-heptan-1-ol

3-Cyclopentyl-2-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

2-(6-Methyl-5-nitro-pyridin-2-ylsulfanyl)-ethanol

[1-(4-Fluoro-3-methyl-phenylamino)-cyclopentyl]-methanol

1-[4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-phenyl]-ethanone

1-{4-((S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl}-ethanone

1-[4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-phenyl]-ethanone

[1-(4-Methanesulfonyl-3-methyl-phenylamino)-cyclopentyl]-methanol

2,2-Dimethyl-3-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

2, 2-Dimethyl-3-(3-methyl-4-nitro-phenylamino)-propan-1-ol

4-((R)-1-Benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

(R)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenylmethanesulfinyl-propan-1-ol

4-((R)-2-Hydroxy-1-phenylmethanesulfinylmethyl-ethylamino)-2-trifluoromethyl-benzonitrile

[1-(4-Nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(4-Nitro-phenylamino)-pentan-1-ol

(S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol

[1-(2-Bromo-4-nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(2-Bromo-4-nitro-phenylamino)-pentan-1-ol

(S)-2-(2-Bromo-4-nitro-phenylamino)-4-methyl-pentan-1-ol

or a pharmaceutically acceptable salt thereof.

13. Use of compound according to claim 1, wherein R_1 or R_2 is a C_6 - C_{10} arylthio comprising an aryl-substituted sulfur-containing C_1 - C_{10} alkyl group.

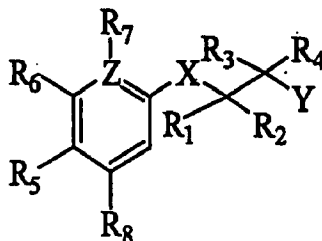
14. Use of a compound according to claim 1, wherein in R_1 or R_2 the alkylsulfur is substituted with a C_6 aryl group.

15. A pharmaceutical composition containing a compound as defined in Formula I of any preceding claim.

16. Use according to claim 1 wherein the disease is caused by an increase in androgen receptor activity.

17. Use according to any of claims 1-14 or 16 wherein the disease is chosen from the group consisting of, prostate cancer, lipid abnormalities, cardiovascular disease and psychological abnormalities, male pattern baldness (alopecia), benign prostatic hyperplasia (BPH) and acne, hirsutism, amenorrhea, hypogonadism, anemia, diabetes, defects in spermatogenesis, cachexia, osteoporosis, osteopenia, and muscle wasting.

18. A compound as defined by Formula I :



Formula I

in which;

R₁ and R₂ are the same or different and independently selected from the group consisting of; hydrogen, halogen, C₁-C₁₀ alkyl, C₁-C₁₀ substituted alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkenoxy, C₁-C₁₀ alkynoxy, C₁-C₁₀ alkylthio, C₁-C₁₀ alkenylthio, C₁-C₁₀ alkynylthio, C₆-C₁₀ arylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarythio, C₁-C₁₀ alkylarylsulphone, C₁-C₁₀ alkylarylsulphoxide, C₆-C₁₀ aryl, or C₃-C₂₀ heteroaryl, optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different; or R₁ and R₂ may together form a C₃-C₁₀ cycloalkyl group;

R₃ and R₄ are the same or different and independently selected from hydrogen, halogen, C₁-C₂₀ alkyl, C₃-C₇ cycloalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₄ alkoxy, C₁-C₄ alkenoxy, C₁-C₄ alkynoxy, C₁-C₄ alkylthio, C₁-C₄ alkenylthio, C₁-C₄ alkynylthio, C₁-C₁₀ alkylsulphone, C₁-C₁₀ alkenylsulphone, C₁-C₁₀ alkynylsulphone, C₆-C₁₀ arylsulphone, C₁-C₁₀ alkylsulphoxide, C₁-C₁₀ alkenylsulphoxide, C₁-C₁₀ alkynylsulphoxide, C₆-C₁₀ arylsulphoxide, C₁-C₁₀ alkylarythio, C₁-C₁₀ alkylarylsulphone, C₁-C₁₀

alkylarylsulphoxide, C₆-C₁₅ aryl, C₅-C₂₀ heteroaryl optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different; or can together form a keto group;

R₅ is chosen from the group consisting of; nitro, cyano, -CH₂CN, -COMe, acetic acid, halogen, sulphonic acid, -SO₂CH₃, aldehyde, carboxylic acid or ester, phosphonic acid or ester;

R₆ is chosen from the group consisting of; hydrogen, C₁-C₅ alkyl, halogen, CN, CO₂H, CHF₂, CH₂F or CF₃;

R₇ is chosen from the group consisting of; H, halogen or C₁-C₅ alkyl;

R₈ is chosen from the group consisting of; hydrogen, C₁-C₅ alkyl, halogen, CHF₂, CH₂F or CF₃;

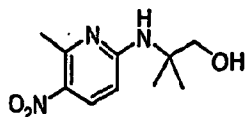
X is chosen from the group consisting of; -NH-, -O-, -S-, -SO-, -SO₂-, -Se-, -Te- or -S-S-

Y is chosen from the group consisting of; hydrogen, hydroxy, -CH₂OH, methoxy, NH₂, unbranched, branched or cyclic C₁-C₅ alkyl, unbranched, branched or cyclic -NH(C₁-C₅ alkyl); unbranched, branched or cyclic N(C₁-C₅ alkyl)₂, -NH(C₆aryl), -N(C₆aryl)₂, -NH(C₁-C₁₀ heteroaryl), and -N(C₅-C₁₀ heteroaryl)₂, C₅-C₁₀ heteroaryl wherein any of said aryl or heteroaryl groups are optionally substituted with up to 3 groups of R^a which groups may be the same or different;

Z is chosen from the group consisting of; C, N, or O;

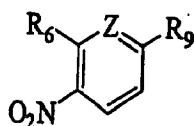
R^a represents a member selected from: hydrogen, halogen, -CN, OH, CO₂H, CHO, NO₂, -NH₂, -NH(C₁-C₄), N(C₁-C₄)₂, -NH(C₆aryl), -N(C₆aryl)₂, -NH(C₅-C₁₀ heteroaryl), and -N(C₅-C₁₀ heteroaryl)₂; or a pharmaceutically acceptable salt thereof.

with the proviso that the compound is not:

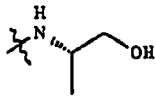
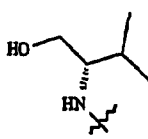
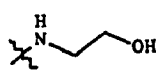
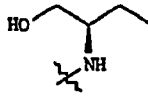
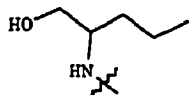
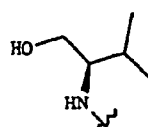
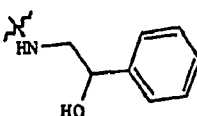
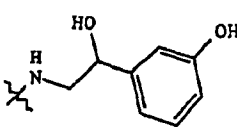


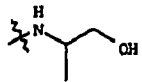
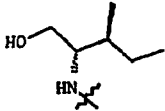
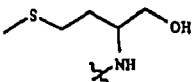
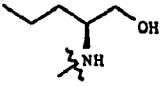
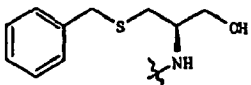
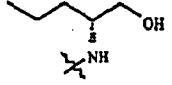
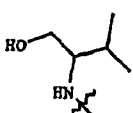
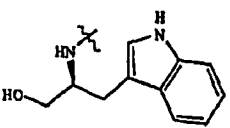
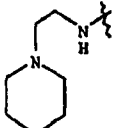
19. A compound according to claim 18, wherein R_1 or/and R_2 are H, (S)-methyl, methyl, (R)-ethyl, (S)-ethyl, ethyl, (R)-propyl, (S)-propyl, propyl, (S)-butyl, (S)-1-methyl-propyl, (S)-2-methyl-propyl, (R)-isopropyl, (S)-isopropyl, isopropyl, cyclopentyl, $-(CH_2)_2SMe$, (R)- CH_2SCH_2Ph , (S)-benzyl, 4-chloro-benzyl, (S)-3-methyl-1-H-indole or (S)-phenyl;
20. A compound according to either of claims 18 and 19, wherein R_3 is chosen from the group consisting of: hydrogen, methyl, ethyl, phenyl, 3-hydroxy phenyl, 4-hydroxy phenyl, or forms a keto group together with R_4 .
21. A compound according to any of claims 18-20, wherein R_4 is H, methyl, or forms a keto group together with R_3 .
22. A compound according to any of claim 18-21, wherein R_5 is NO_2 , CN , CH_2CN or CO_2H ;
23. A compound according to any of claims 18-22, wherein R_6 is Me, or CF_3 .
24. A compound according to any of claims 18-23, wherein R_7 is H or Me.
25. A compound according to any of claims 18-24, wherein R_8 is H or methyl.
26. A compound according to any of claims 18-25, wherein X is NH.
27. A compound according to any of claims 18-26, wherein Y is H, -OH, -OMe, -N $(CH_2CH_3)_2$, piperidine, or 4-nitro-2-ylamino.
28. A compound according to any of claims 18-27, wherein Z is CR_7 or N.
29. A compound according to any of claims 18-28, wherein the compound is chosen from the group consisting of:

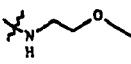

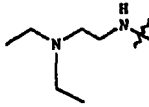

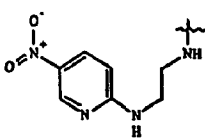
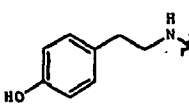
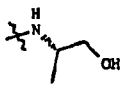
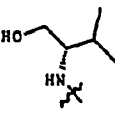
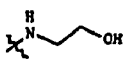
2-Methyl-2-(4-nitro-3-trifluoromethyl-phenylamino)-propan-1-ol;
 [1-(4-Nitro-3-trifluoromethyl-phenylamino)-cyclopentyl]-methanol;
 (S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-3-phenyl-propan-1-ol;
 (S)-2-(4-Nitro-3-trifluoromethyl-phenylamino)-butan-1-ol;
 2-Methyl-2-(3-hydroxy-4-nitro-phenylamino)-propan-1-ol;
 [1-(3-Methyl-4-nitro-phenylamino)-cyclopentyl]-methanol;
 (S)-2-(3-Methyl-4-nitro-phenylamino)-butan-1-ol;
 2-Methyl-2-(6-methyl-5-nitro-pyridine-2-ylamino)-propan-1-ol;
 [1-(6-Methyl-5-nitro-pyridine-2-ylamino)-cyclopentyl]-methanol;
 (S)-2-(6-Methyl-5-nitro-pyridine-2-ylamino)-2-phenyl-ethanol;
 (S)-2-(6-Methyl-5-nitro-pyridine-2-ylamino)-3-phenyl-propan-1-ol;
 (S)-2-(6-Methyl-5-nitro-pyridine-2-ylamino)-butan-1-ol;
 (DL)-3-(4-Chloro-phenyl)-2-(6-methyl-5-nitro-pyridine-2-ylamino)-propan-1-ol;
 (S)-2-(6-Methyl-5-nitro-2-pyridin-ylamino)-propionic acid;
 (S)-2-(6-Methyl-5-nitro-pyridine-2-ylamino)-propan-1-ol;
 2-(2,3-Dimethyl-4-nitro-phenylamino)-2-methyl-propan-1-ol;
 (S)-2-(3,5-Dimethyl-4-nitro-phenylamino)-butan-1-ol;
 4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-trifluoromethyl-benzonitrile;
 4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
 (S)-4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-benzonitrile;
 (R)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;
 (S)-4-(1-Hydroxymethyl-butylamino)-2-trifluoromethyl-benzonitrile;
 [4-((S)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
 [4-((R)-1-Hydroxymethyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
 [4-((S)-1-Hydroxymethyl-3-methyl-butylamino)-2-trifluoromethyl-phenyl]-acetonitrile;
 4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-benzonitrile;
 6-(2-Hydroxy-1,1-dimethyl-ethylamino)-2-methyl-nicotinonitrile;
 4-(2-Hydroxy-1,1-dimethyl-ethylamino)-2,3-dimethyl-benzonitrile;
 and compounds having the formula:

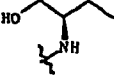
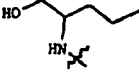
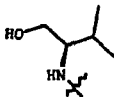
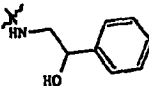
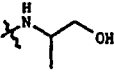
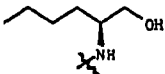
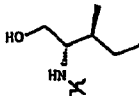
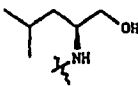
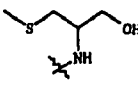


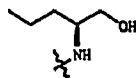
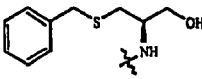
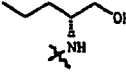
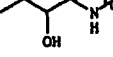

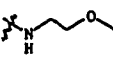


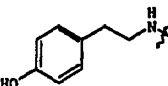
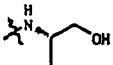
in which R₉, R₆ and Z are as defined in the following table:

R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH

R9	R6	Z		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		
	CF ₃	CH		

R9	R6	Z
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CF ₃	CH
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N

R9	R6	Z
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	N
	CH ₃	CH

[illegible]

1-[4-(1-Hydroxymethyl-cyclopentylamino)-2-trifluoromethyl-phenyl]-ethanone

[1-(4-Methanesulfonyl-3-methyl-phenylamino)-cyclopentyl]-methanol

2,2-Dimethyl-3-(6-methyl-5-nitro-pyridin-2-ylamino)-propan-1-ol

2, 2-Dimethyl-3-(3-methyl-4-nitro-phenylamino)-propan-1-ol

4-((R)-1-Benzylsulfanylmethyl-2-hydroxy-ethylamino)-2-trifluoromethyl-benzonitrile

(R)-2-(6-Methyl-5-nitro-pyridin-2-ylamino)-3-phenylmethanesulfinyl-propan-1-ol

4-((R)-2-Hydroxy-1-phenylmethanesulfinylmethyl-ethylamino)-2-trifluoromethyl-benzonitrile

[1-(4-Nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(4-Nitro-phenylamino)-pentan-1-ol

(S)-4-Methyl-2-(4-nitro-phenylamino)-pentan-1-ol

[1-(2-Bromo-4-nitro-phenylamino)-cyclopentyl]-methanol

(S)-2-(2-Bromo-4-nitro-phenylamino)-pentan-1-ol

(S)-2-(2-Bromo-4-nitro-phenylamino)-4-methyl-pentan-1-ol

30. A compound according to any of claims 18-29, wherein R_1 or R_2 is a C_6 - C_{10} arylthio comprising an aryl-substituted sulfur-containing C_1 - C_{10} alkyl group.

31. A compound according to any of claims 18-30, wherein in R_1 or R_2 the alkylsulfur is substituted with a C_6 aryl group.

Internal Application No
PCT/GB2004/004464

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07C205/11	C07C255/50	C07C323/25	C07D213/74	A61K31/04
	A61K31/435	A61K31/277	A61K31/10	A61P5/28	

B. FIELDS SEARCHED

IPC 7 C07C C07D A61K A61P

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/58854 A (BIOPHYSICA, INC) 16 August 2001 (2001-08-16) page 4, line 22 - page 5, line 3 claim 1	1-31
A	WO 02/16310 A (GTX, INC; DALTON, JAMES; MILLER, DUANE, D; YIN, DONGHUA; HE, YALI) 28 February 2002 (2002-02-28) claims 12,14,16,18,26 ----- -/--	1-31

☒ Patent family members are listed in annex.

"&" document member of the same patent family

18/03/2005

Goetz, G

INTERNATIONAL SEARCH REPORT

 Int. Application No
 PCT/GB2004/004464

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KELLER, HELMUT ET AL: "Oxidative hair dye composition comprising a 2,5-diaminobenzonitrile" XP002320584 retrieved from STN Database accession no. 127:311348 see RN 197382-91-5 abstract & EP 0 797 980 A1 (WELLA A.-G., GERMANY) 1 October 1997 (1997-10-01)	18-28
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HASHIZUME, KAZUNARI ET AL: "Oxidizable color-producing reagents containing p-fluoroaniline derivatives" XP002320585 retrieved from STN Database accession no. 117:127839 see RN 143205-22-5 abstract & EP 0 488 756 A1 (WAKO PURE CHEMICAL INDUSTRIES, LTD., JAPAN) 3 June 1992 (1992-06-03)	18-21
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TEACH, EUGENE G.: "Herbicidal oxazolidines and methods of use" XP002320586 retrieved from STN Database accession no. 108:217796 see RN 114010-11-6 abstract & US 4 723 986 A (TEACH, EUGENE G.) 9 February 1988 (1988-02-09)	18-21
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SUDA, HIDEAKI ET AL: "p-Nitroaniline derivatives" XP002320587 retrieved from STN Database accession no. 81:25336 see RN 52177-12-5 abstract & JP 49 020129 A2 (SUMITOMO CHEMICAL CO., LTD.) 22 February 1974 (1974-02-22)	18-28
	-/-	

INTERNATIONAL SEARCH REPORT

Inte Patent Application No
PCT/GB2004/004464

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ZORINA, L. N. ET AL: "New approach to the synthesis of N-aryl-1,3-oxazolidines and N-aryl-1,3-tetrahydrooxazines" XP002320588 retrieved from STN Database accession no. 112:216820 see RN 126993-10-0 abstract & DOKLADY AKADEMII NAUK SSSR , 308(5), 1150-4 'CHEM.' CODEN: DANKAS; ISSN: 0002-3264, 1989,</p> <p style="text-align: center;">-----</p>	18-21

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/GB2004/004464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0158854	A	16-08-2001	US 6472415 B1 29-10-2002
			AT 259781 T 15-03-2004
			AU 3685601 A 20-08-2001
			AU 5302600 A 20-08-2001
			BR 0008439 A 23-04-2002
			CA 2400185 A1 16-08-2001
			CN 1416416 A 07-05-2003
			CZ 20012398 A3 14-11-2001
			DE 10084380 T0 20-06-2002
			DE 60008360 D1 25-03-2004
			DE 60008360 T2 09-12-2004
			EP 1169301 A1 09-01-2002
			ES 2215672 T3 16-10-2004
			ES 2187390 A1 01-06-2003
			JP 2003522752 T 29-07-2003
			PL 350356 A1 02-12-2002
			RU 2225390 C2 10-03-2004
			WO 0158854 A1 16-08-2001
			WO 0158855 A1 16-08-2001
			ZA 200206497 A 14-08-2003
WO 0216310	A	28-02-2002	AU 8523001 A 04-03-2002
			BR 0114801 A 14-10-2003
			CA 2420279 A1 28-02-2002
			CN 1471508 A 28-01-2004
			EP 1401801 A1 31-03-2004
			EP 1491524 A2 29-12-2004
			JP 2004518617 T 24-06-2004
			WO 0216310 A1 28-02-2002
			US 2002099036 A1 25-07-2002
			US 2002099096 A1 25-07-2002
			US 2002173495 A1 21-11-2002
			US 2003022868 A1 30-01-2003
			US 2003162761 A1 28-08-2003
			US 2003232792 A1 18-12-2003
			US 2003225040 A1 04-12-2003
			US 2004014975 A1 22-01-2004
			US 2004260108 A1 23-12-2004
			US 2005038110 A1 17-02-2005
EP 0797980	A1	01-10-1997	DE 19612506 A1 02-10-1997
			BR 9701464 A 25-08-1998
			ES 2109207 T1 16-01-1998
			JP 9268170 A 14-10-1997
			US 5865856 A 02-02-1999
EP 0488756	A1	03-06-1992	JP 2701090 B2 21-01-1998
			JP 4202164 A 22-07-1992
			DE 69124780 D1 03-04-1997
			DE 69124780 T2 16-10-1997
			ES 2097798 T3 16-04-1997
			US 5238818 A 24-08-1993
US 4723986	A	09-02-1988	NONE
JP 49020129	A2	22-02-1974	JP 49020129 A 22-02-1974
			CA 1012553 A1 21-06-1977
			CH 593236 A5 30-11-1977

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/004464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 49020129	A2	DE 2331900 A1	24-01-1974
		FR 2199533 A1	12-04-1974
		FR 2225423 A1	08-11-1974
		GB 1421600 A	21-01-1976
		IT 991637 B	30-08-1975
<hr/>			

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 31/275, C07C 255/61		A1	(11) International Publication Number: WO 99/08673
			(43) International Publication Date: 25 February 1999 (25.02.99)
(21) International Application Number: PCT/US98/16015		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 3 August 1998 (03.08.98)			
(30) Priority Data: 60/055,568 13 August 1997 (13.08.97) US 60/071,364 15 January 1998 (15.01.98) US			
(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).			
(72) Inventor: ATWAL, Karnail, S.; 92 Valley View Way, Newtown, PA 18940 (US).		Published With international search report.	
(74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).			
(54) Title: ENANTIOMERS OF 4-[[[(CYANOIMINO)-[(1,2,2-TRIMETHYLPROPYL) AMINO]METHYL]AMINO] BENZONITRILE			
(57) Abstract			
The (R)-enantiomer of 4-[[[(cynnoimino)-[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile as well as the corresponding (S)-enantiomer are useful for promoting hair growth such as in male pattern baldness.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SE	Sweden
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	ME	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	NL	Netherlands	TR	Turkey
BG	Bulgaria	HU	Hungary	NM	Norway	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	NP	Nepal	UA	Ukraine
BR	Brazil	IL	Israel	NR	Nauru	UG	Uganda
BY	Belarus	IS	Iceland	NW	Niger	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LE	Sierra Leone	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

WO 99/08673

PCT/US98/16015

ENANTIOMERS OF 4-[[[(CYANOIMINO)[(1,2,2-
TRIMETHYL-PROPYL)AMINO]METHYL]AMINO]BENZONITRILE

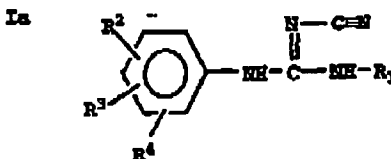
Field of the Invention

5 The present invention relates to the (R)-
and (S)-enantiomers of 4-[[[(cyanoimino)[(1,2,2-
trimethyl-propyl)amino]methyl]amino]benzonitrile,
pharmaceutical compositions containing same, and a
method for promoting hair growth employing such
10 enantiomers.

Background of the Invention

Potassium channel openers such as minoxidil
(Upjohn), pinacidil (Lilly) and diazoxide (Shiseido
15 and Schering-Plough) are known for their hair
growth stimulating activity. Thus, U.S. Patent
Nos. 4,596,812 and 4,139,619 disclose use of
minoxidil in the treatment of male pattern
baldness, alopecia areata and balding in females.
20 U.S. Patent No. 4,057,636 discloses pinacidil.
DE 3,827,467A discloses combinations of minoxidil
and hydrocortisone or retinoids.

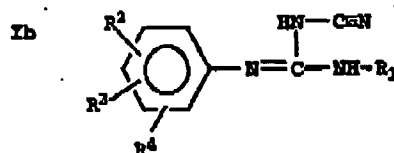
U.S. Patent No. 5,011,837 to Atwal et al
discloses aryl cyanoguanidines which possess
25 potassium channel activating activity and are
useful therapy for hypertension and other
cardiovascular disorders, for various central
nervous system disorders, kidney and urinary
problems as well as for the promotion of hair
30 growth, for example in the treatment of male
pattern baldness (alopecia). These aryl
cyanoguanidines have the structure



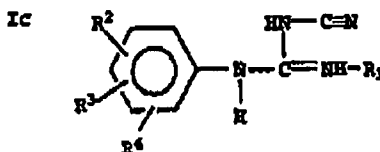
WO 99/08673

PCT/US98/16015

and its possible tautomers



and



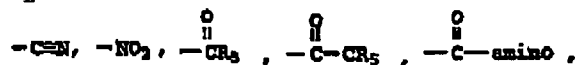
5

including pharmaceutically acceptable salts,
wherein

R₁ is alkyl, alkenyl, alkynyl, haloalkyl,
cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;

10

R₂ is



R₃ and R₄ are each independently selected
15 form -R₂, hydrogen, alkyl, alkenyl, alkynyl,
haloalkyl, halo, alkoxy, -NHalkyl, -N-(alkyl)₂, -S-
alkyl, -O-aryl-alkyl, -S-arylalkyl or -S-aryl, -O-
aryl, -NHaryl-alkyl, or R₂ and R₃ taken together
are a group which form a ring with the two carbon
20 atoms to which they are attached, which group is
selected from



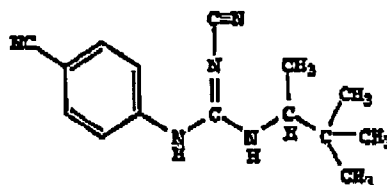
wherein

25 m=1 or 2,
n=3-5,
p=2-4,
X is O, NR₅, CH₂; and
R₅ is hydrogen or R₁.

WO 99/08673

PCT/US98/16015

Example 1 of U.S. Patent No. 5,011,837 discloses the preparation of 4-[[[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]benzonitrile



5

in the form of its racemic mixture.

PCT Application WO 92/02225 discloses a combination of a potassium channel opener and a 5- α -reductase inhibitor for promoting hair growth.

10

PCT Application WO 92/09259A discloses use of an androgen blocker and a potassium channel activator for stimulation of hair growth.

Description of the Invention

15

In accordance with the present invention, it has been unexpectedly found that the (R)-enantiomer of 4-[[[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile, including

20

pharmaceutically acceptable salts, thereof exhibits remarkable hair growth promoting activity which is superior in such regard to the corresponding (S)-enantiomer and the racemic mixture of such enantiomers. In fact, it has been found that the (R)-enantiomer is surprisingly and unexpectedly

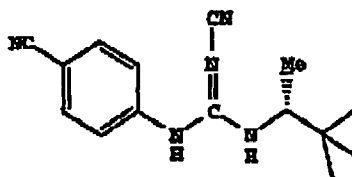
25

more effective in stimulating hair follicles to produce hair growth at a substantially faster rate as compared to the corresponding (S)-enantiomer.

The above (R)-enantiomer of the invention has the structure I

30

I



WO 99/08673

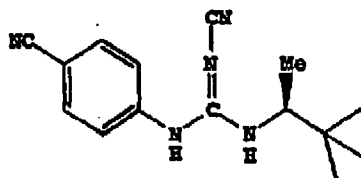
PCT/US98/16013

The (R)-enantiomer I will be in substantially pure form, that is, will be at least 99% pure (R)-enantiomer and will at most contain 1% (S)-enantiomer.

- 5 In addition, in accordance with the present invention, it has been found that the (S)-enantiomer of 4-[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile, including pharmaceutically acceptable salts thereof, exhibits
10 excellent hair growth promoting activity.

The above (S)-enantiomer of the invention has the structure II

II



- 15 The (S)-enantiomer II will be in substantially pure form, that is, will be at least 99% pure (S)-enantiomer and will at most contain 1% (R)-enantiomer.

- The enantiomers of the invention form salts with a variety of inorganic and organic acids. The
20 non-toxic pharmaceutically acceptable salts are preferred, although other salts may also be useful in isolating or purifying the product. Such pharmaceutically acceptable salts include those
25 formed with hydrochloric acid, methanesulfonic acid, sulfuric acid, acetic acid, maleic acid, and the like. The salts are obtained by reacting the product with an equivalent amount of the acid in a medium in which the salt precipitates.

- 30 The present invention also includes pharmaceutical compositions containing the (R)-enantiomer of 4-[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile or a

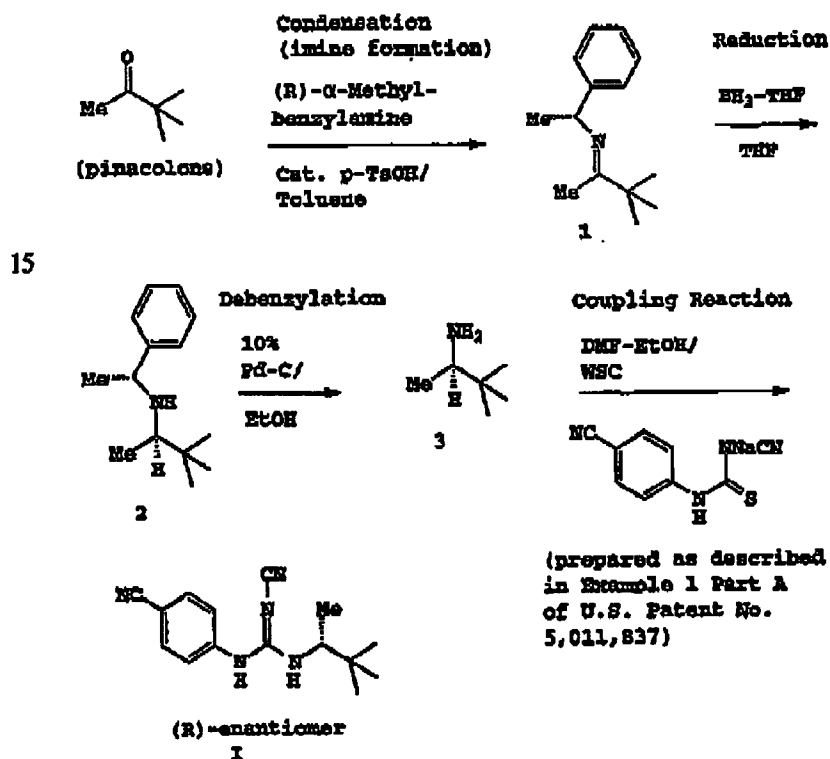
WO 99/08673

PCT/US98/16015

pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

In addition, the present invention also includes pharmaceutical compositions containing the
 5 (S)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

The (R)-enantiomer of the invention, that
 10 is, (R)-4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)-amino]methyl]amino]benzonitrile may be prepared according to the following reaction sequence:

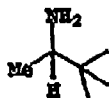


The (S)-enantiomer of the invention, that is
 (S)-4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)-
 amino]methyl]amino]benzonitrile may be prepared
 20 according to the above reaction sequence for preparation of the (R)-enantiomer except that (S)-

WO 99/08673

PCT/US98/16015

α -methylbenzylamine is employed in place of (R)- α -methylbenzylamine to eventually form



- 5 which is reacted with the 4-cyano-N'-(4-cyanophenyl)thiourea, monosodium salt to form the (S)-enantiomer (II).

- The (R)-enantiomer I of the invention or the
10 (S)-enantiomer II of the invention may be formulation with other hair growth promoting compounds such as the potassium channel openers minoxidil (Upjohn) and/or diazoxide (Shiseido and Schering-Plough), as well as cromakalim and
15 pinacidil; a 5- α -reductase inhibitor such as finasteride (Merck's Proscar[®]), terazosin HCl (Abbott's Hytrin[®]), or doxazosin mesylate (Pfizer's Cardura[®]); and/or an androgen blocker such as 4-(5-methoxyheptyl)-hexahydro-2(1H)-pentalenone as
20 disclosed in PCT Application WO 92/09259A, vasoconstrictors such as betamethasone dipropionate, corticosteroids such as hydrocortisone, and scopolamine, and cyproterone acetate.

- 25 The enantiomers of the invention may be administered via topical, oral, parenteral or rectal routes as described in U.S. Patent No. 5,011,837 (incorporated herein by reference), with topical being preferred. Thus, the enantiomers of
30 the invention in suitable topical formulations are applied to the skin region where hair growth is desired.

- Typical topical formulations for use herein will include conventional ointments, creams,
35 lotions, waxes, gels, pastes, jellies, sprays, aerosols and the like in aqueous or non-aqueous

WO 99/08673

PCT/US98/16015

formulations. Examples of suitable topical formulations are disclosed in U.S. Patent Nos. 4,139,619 and 4,596,812 which are incorporated herein by reference.

- 5 The enantiomers of the invention will be used in an effective amount, that is, in an amount sufficient to promote hair growth or treat hair growth disorders, such that hair growth is increased or produced. A typical topical
- 10 composition will include from about 0.01 to about 15% by weight, preferably from about 0.1 to about 10% by weight of the composition.

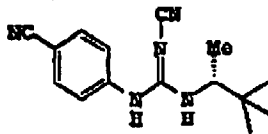
- The topical formulations containing the enantiomers of the invention can be applied to the
- 15 area to be treated such as the scalp in humans, by spraying, dabbing or swabbing to deliver the enantiomer to the region of the hair follicle. The formulations will be applied to the area of treatment on a routine basis prior to, during and
- 20 subsequent to hair growth, at least once daily, and preferably two or more times daily.

- The accompanying Figure is a graph showing the effect of a once daily application of each of the (R)- and (S)- enantiomers described herein on
- 25 hair growth in male C3H mice.

 The following Examples represent preferred embodiments of the present invention.

Example 1

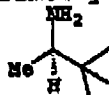
- 30 (R)-4-[[(Cyanoimino) [(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile



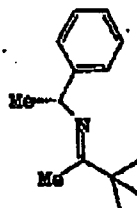
WO 99/08673

PCT/US98/16015

A. (R)-1,2,2-Trimethylpropyl amine



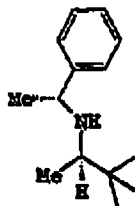
The title compound was prepared according to the procedure described by Manley and Quast (*J. Med. Chem.* 1992, 35, 2327-2340) with some modification. A mixture of pinacolone (29 g, 290 mmol), (R)- α -methylbenzyl amine (17.6 g, 145 mmol) and p-toluenesulfonic acid monohydrate (300 mg) in toluene (150 mL) was refluxed using a Dean-Stark trap (to remove water from the reaction mixture) for 3 days. The solvent was evaporated and the residue was distilled at ca. 120-2°C (9 mm) to give 21 g (71% yield) of



as a colorless oil. This material was dissolved in anhydrous THF (210 mL) and treated at 0-2°C with borane-THF complex (1M, 206 mL, 206 mmol). The mixture was allowed to come to room temperature, stirred for 5h and concentrated *in vacuo*. To the resulting oily residue was carefully added ethanol (300 mL), and the mixture was refluxed for 1h and concentrated again *in vacuo*. The residue was chromatographed over basic alumina (activity grade 1/hexane) giving colorless oil. Proton NMR and HPLC (YMC C18 S3 4.6X50 mm column/water-MeOH-H₃PO₄ 90:10:0.2 to 10:90:0.2 gradient) indicated that this material was contaminated with ca. 10% of the (S,R)-diastereomer. Therefore, this mixture was resubjected to flash chromatography (silica gel/hexane-EtoAc-triethylamine 95:5:0.1) to afford

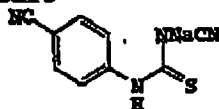
WO 99/08673

PCT/US99/16015



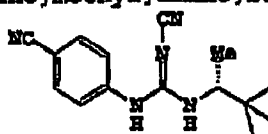
(11.45 g, 55.8 mmol, 54% yield). The above compound (11.45 g) and 10% palladium on carbon (1.5 g) were taken in EtOH (230 mL) and stirred under hydrogen for 12 hours. The mixture was filtered and the filtrate (ca. 230 mL) containing the title product was used as such for the next step as a ca. 0.24 M solution in ethanol (assumed 100% yield).

10 B. N-Cyano-N'-(4-cyanophenyl)thiourea, monosodium salt



The title compound was prepared according to Example 1 Part A of U.S. Patent No. 5,011,837.

C. (R)-4-[[[(Cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile



20 To a solution of Part B compound (6.0 g, 26.8 mmol) in DMF (150 mL) was sequentially added the solution of Part A compound (ca. 0.24 M in EtOH, 112 mL, 26.8 mmol) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (WSC) (6.0 g, 31.3 mmol). The mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate and sequentially washed with 1N HCl, water and brine. The organic layer was dried over

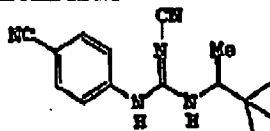
WO 99/08673

PCT/US98/16015

- magnesium sulfate, concentrated and the crude product was purified by flash chromatography on silica gel (hexanes-ethyl acetate-triethylamine 75:25:0.2) to afford a colorless foam. This material was recrystallized from isopropanol to give the title compound as a white solid (4.15 g, 57.6%), mp 159-60°C; $[\alpha]_D^{25} -180^\circ$ C=1, MeOH; enantiomeric purity determined by chiral HPLC = 99% (ChiralPak AD column/hexane-isopropanol-triethylamine 80:20:0.2); MS: 270 (M+H)⁺; ¹H NMR (CDCl₃) δ 8.65 (br s, 1H), 7.69 (d, 2H, J=8.79 Hz), 7.37 (d, 2H, J=8.79 Hz), 4.93 (br d, 1H), 3.83 (m, 1H), 1.10 (d, 1H, J=6.45 Hz), 0.90 (s, 9H).
- 15 Elemental analysis: calculated for C₁₅H₁₉N₅:
C, 66.89; H, 7.11; N, 26.00
Found: C, 66.71; H, 7.14; N, 25.98.

Example 2

- 20 (S)-4-[[[(Cyanoimino)[(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile



- 25 The title compound was prepared from Part B compound of Example 1 and (S)-1,2,2-trimethylpropyl amine (prepared according to Manley and Quast, *J. Med. Chem.*, 1992, 35, 2327-2340) by the same procedure as described in Example 1, Part C. The product was obtained as a colorless solid, mp 158-59°C; $[\alpha]_D^{25} +189^\circ$ C=1, MeOH; enantiomeric purity determined by chiral HPLC = 99.4% (ChiralPak AD column/hexane-isopropanol-triethylamine 80:20:0.2); MS: 270 (M+H)⁺; ¹H NMR (CDCl₃) δ 8.43 (br s, 1H), 7.69 (d, 2H, J=8.79 Hz), 7.37 (d, 2H, J=8.79 Hz),
- 35

WO 99/08673

PCT/US98/16015

4.93 (br d, 1H), 3.83 (m, 1H), 1.10 (d, 1H, J=6.45 Hz), 0.90 (s, 9H).

Example 3

5 Comparison of Example 1-(R)-Enantiomer and Example 2-(S)-Enantiomer Re Hair Growth in an Animal Model

The objective of the following described experiment was to compare and evaluate the in vivo effect of the Example 1-(R)-enantiomer and the Example 2-(S)-enantiomer on hair growth in an animal model. The two enantiomers were compared topically for hair growth in C3H mice.

15 Animal Model

The C3H mouse is a useful model for studying hair growth. Its usefulness rests with the fact that skin pigmentation of this animal is provided by the melanocytes of the hair follicle and not the epidermis. In the telogen or the resting phase of the hair follicle, the skin is pink. In the earliest phase of anagen or the growth phase, there is sudden graying of the skin and as the anagen phase progresses the skin becomes darker in color. In this study, visual observation was used as an in vivo assay of anagen induction. Furthermore as anagen develops, the skin thickness increases from a thin telogen skin to a measurably thickened anagen skin. Thus, recording the skin color and microscopic thickness of skin from these mice offers a sensitive, quantifiable and convenient method of assessing the phases of hair growth.

Groups of 20, six to seven week old male C3H mice with hair follicles in the resting phase of hair growth were used. At this stage in their life, the hair follicles remain in the telogen phase for up to 30 days or longer. This provides

WO 99/08673

PCT/US98/16815

an adequate window of time to screen drugs. Compounds that improve hair growth stimulate the hair follicles from the telogen to the anagen phase. This stimulation is manifested by the shortening of the telogen phase of the hair follicle cycle.

Animals were anesthetized with ketamine/ rompun (100 mg/Kg and 12 mg/Kg) IP and the hair over a defined dorsal area were closely clipped.

Animals with pink skin were treated topically 1x daily, 5 days per week with 50 microliters of a 2% solution of Example 1-(R)-enantiomer and a 2% solution of Example 1-(S)-enantiomer or vehicle by itself, applied to the dorsal area. The vehicle employed was ethanol/propylene glycol/water, 60/30/10. Treatment was continued for at least 4-5 weeks.

Animals were observed daily for side effects and changes to the test sites. All observations were documented. Test sites were graded weekly for changes in skin color and hair growth. In this study drug effects were evaluated using the visual observation of skin changing from pink to gray and resulting in hair growth.

Results

The percent of animals that induced hair follicle stimulation during the treatment period is illustrated in the accompanying Figure below. The most significant observation made between the two enantiomers is the difference in the time of onset of follicle stimulation. The time of onset for the Example 1-(R)-enantiomer was day 7 compared to day 11 for Example 2-(S)-enantiomer. The time of onset for the vehicle control was day 28. By day 11 of treatment the Example 1-(R)-enantiomer caused hair follicle stimulation in 40% of the test mice

WO 99/08673

PCT/US98/16015

compared to only 5% with Example 2-(S)-enantiomer. By day 14, 50% of the animals treated with Example 1-(R)-enantiomer showed hair follicle stimulation compared to 25% for Example 2-(S)-enantiomer. By
5 day 28, 85% of the animals treated with the Example 1-(R)-enantiomer showed hair follicle stimulation as compared to 65% treated with Example 2-(S)-enantiomer. Thus throughout the treatment period, the group treated with Example 1-(R)-enantiomer
10 showed a higher incidence of hair follicle stimulation as compared to the group treated with Example 2-(S)-enantiomer.

The attached Figure shows the effect of 1x daily topical application of Example 1-(R)-
15 enantiomer and Example 2-(S)-enantiomer.

In conclusion, these results in the C3H mice indicate that there is a remarkable difference between the Example 1-(R)-enantiomer and the Example 2-(S)enantiomer in their effect on hair
20 follicle stimulation; in particular the (R)-enantiomer has a faster onset of action compared to the corresponding (S)-enantiomer.

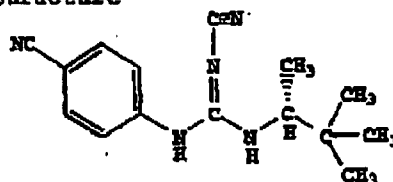
These results are indeed surprising and unexpected especially in view of the vasorelaxant
25 potencies of each of these enantiomers, which is generally recognized as an indication of hair growth promoting properties (Side Effects of Vasodilator Therapy, W.A. Pettinger et al, Hypertension, 1988, Vol. 11, II-34 to II-36, and
30 Minoxidil Stimulates Cutaneous Blood Flow in Human Balding Scalps: Pharmacodynamics measured by laser Doppler velocimetry and photopulse plethysmography. R.C. Wester et al, J. Invest. Dermatol., 184, Vol. 82, 515-517).

WO 99/08673

PCT/US98/16015

What is Claimed is:

1. The (R)-enantiomer of 4-[[[(cyanoimino)-
[(1,2,2-trimethylpropyl)amino]methyl]amino]-
benzonitrile or a pharmaceutically acceptable salt
5 thereof.
2. The (R)-enantiomer as defined in Claim 1
substantially separated from its corresponding S-
enantiomer.
3. The (R)-enantiomer as defined in Claim 1
10 having the structure



in substantially pure form.

4. The (R)-enantiomer as defined in Claim 1
having an enantiomeric purity equal to at least
15 99%.
5. A pharmaceutical composition comprising
the (R)-enantiomer as defined in Claim 1 and a
pharmaceutically acceptable carrier therefor.
6. A pharmaceutical combination which
20 comprises the R-enantiomer as defined in Claim 1 in
combination with another hair growth promoting
agent.
7. A method for promoting hair growth which
comprises administering to a human in need of
25 treatment a therapeutically effective amount of the
(R)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-
trimethylpropyl)amino]methyl]amino]benzonitrile or
a pharmaceutically acceptable salt thereof.
8. The method as defined in Claim 7 wherein
30 the (R)-enantiomer is administered systemically or
topically.
9. The method as defined in Claim 7 wherein
the (R)-enantiomer is administered topically.

WO 99/08673

PCT/US98/16015

Thus, while the IC_{50} for vasorelaxant potency of the (R)-enantiomer is 47 ± 17 nM versus 157 ± 35 nM for the (S)-enantiomer, as seen above, the hair growth promoting ability of the (R)-
5 enantiomer for producing hair growth within 11 days of treatment is 8 times greater than the corresponding (S)-enantiomer.

WO 99/08673

PCT/US98/16015

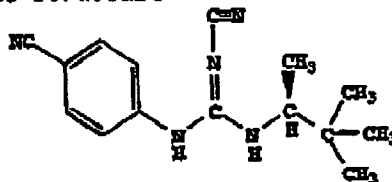
10. The method as defined in Claim 7 wherein the (R)-enantiomer is administered as a cream formulation, lotion formulation, liquid formulation or ointment formulation.

5 11. A method for treating male pattern baldness which comprises administering to a human in need of treatment a therapeutically effective amount of the R-enantiomer as defined in Claim 1.

12. The (S)-enantiomer of 4-[[[(cyanoimino)-
10 [(1,2,2-trimethylpropyl)amino]methyl]amino]-benzonitrile or a pharmaceutically acceptable salt thereof.

13. The (S)-enantiomer as defined in Claim 12 substantially separated from its corresponding
15 (R)-enantiomer.

14. The (S)-enantiomer as defined in Claim 12 having the structure



in substantially pure form.

20 15. The (S)-enantiomer as defined in Claim 12 having an enantiomeric purity equal to at least 99%.

16. A pharmaceutical composition comprising the (S)-enantiomer as defined in Claim 12 and a
25 pharmaceutically acceptable carrier therefor.

17. A pharmaceutical combination comprising the S-enantiomer as defined in Claim 12 in combination with another hair-growth promoting agent.

30 18. A method for promoting hair growth which comprises administering to a human in need of treatment a therapeutically effective amount of the (S)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-

WO 99/08673

PCT/US98/16015

trimethylpropyl)amino]methyl]amino]benzonitrile or
a pharmaceutically acceptable salt thereof.

19. The method as defined in Claim 18
wherein the (S)-enantiomer is administered
5 systemically or topically.

20. The method as defined in Claim 18
wherein the (S)-enantiomer is administered
topically.

21. The method as defined in Claim 18
10 wherein the (S)-enantiomer is administered as a
cream formulation, lotion formulation, liquid
formulation or ointment formulation.

22. A method for treating male pattern
baldness which comprises administering to a human
15 in need of treatment a therapeutically effective
amount of the (S)-enantiomer as defined in Claim
12.

WO 99/08673

PCT/US98/16015

1/1

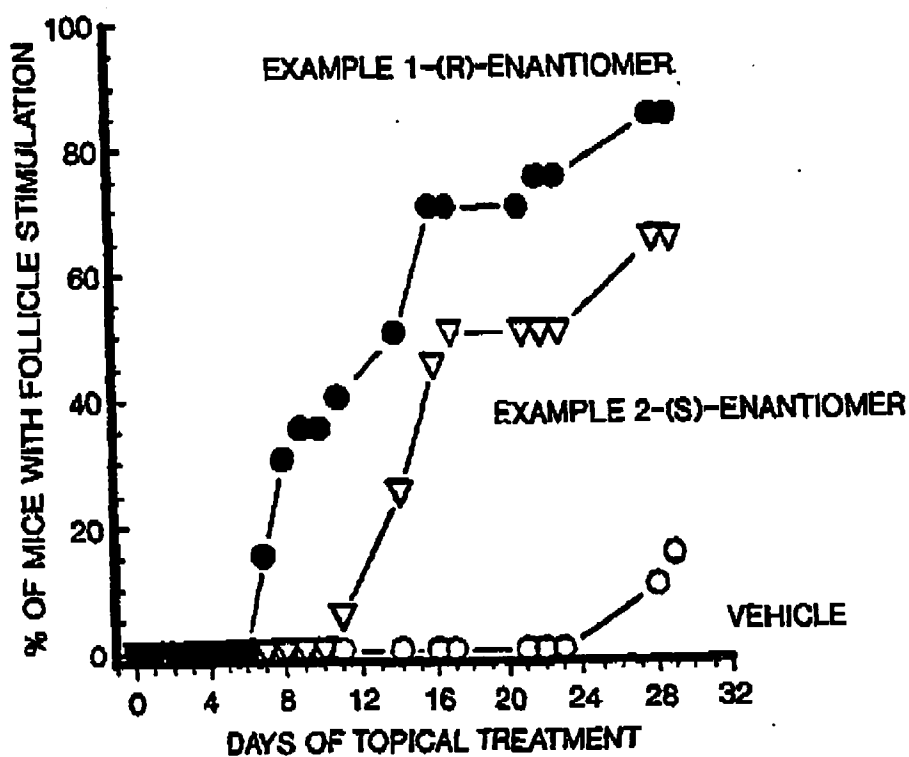


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16015

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/275; C07C 255/61

US CL : 514/524; 558/419

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/524; 558/419

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,011,837 A (ATWAL et al.) 30 April 1991, see entire document.	1-22
Y	US 5,578,599 A (DIANI et al.) 26 November 1996, see entire document.	1-22
Y	WO 92/09259 A1 (THE UPJOHN COMPANY) 11 June 1992, see entire document.	1-22

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* B* earlier document published on or after the international filing date	* Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* C* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* Z*	document member of the same patent family
* D* document referring to an oral disclosure, use, exhibition or other means		
* E* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 SEPTEMBER 1998

Date of mailing of the international search report

22 OCT 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

PETER G. O'SULLIVAN

Telephone No. (703) 308-1235

⑩ BUNDESREPUBLIK
DEUTSCHLAND



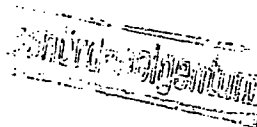
DEUTSCHES
PATENTAMT

⑫ Offenlegungsschrift
⑪ DE 3825 170 A1

⑳ Aktenzeichen: P 38 25 170.1
㉑ Anmeldetag: 23. 7. 88
㉒ Offenlegungstag: 25. 1. 90

⑤ Int. Cl. 5:
C07D 413/12

C 07 D 261/08
C 07 D 261/12
A 61 K 31/42
// C07D 413/12,
261:06,263:30



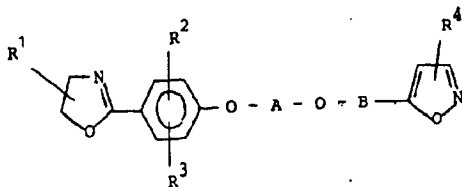
DE 3825 170 A1

㉗ Anmelder:
Hoechst AG, 6230 Frankfurt, DE

㉘ Erfinder:
Sinharay, Akhileswar, Dr., 6000 Frankfurt, DE;
Winkler, Irvin, Dr., 6237 Liederbach, DE; Helsberg,
Matthias, Dr., 6233 Kelkheim, DE

- ⑤4 Substituierte 5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxyalkylenoxyalkyl]-isoxazole, Verfahren sowie 5-(Phenoxyalkylenoxyalkyl)-isoxazole als Zwischenprodukte zu ihrer Herstellung und ihre Verwendung zur Bekämpfung von Krankheiten, die durch Infektion mit Viren hervorgerufen wurden

Neue Isoxazol-Derivate der Formel



in der die Substituenten R¹ bis R⁴ sowie A und B die genannten Bedeutungen haben, eignen sich zur Bekämpfung von Krankheiten, die durch Infektion mit Viren, insbesondere mit Picornaviren, hervorgerufen worden sind.

DE 3825 170 A1

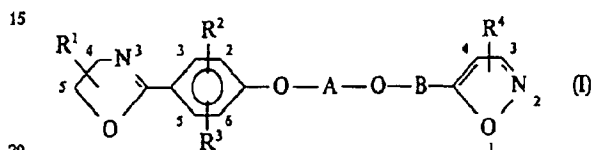
BEST AVAILABLE COPY

Beschreibung

Die Bekämpfung von Virus-Infektionen bzw. durch diese hervorgerufenen Krankheiten (Viruserkrankung) mit chemotherapeutischen Mitteln ist wichtig, weil vielen Viruserkrankungen mit einer Impfung nicht vorgebeugt werden kann, da die betreffenden Virustypen häufig ihre Hülle ändern. Gegen zahlreiche Viruserkrankungen sind bereits Chemotherapeutika beschrieben worden; z. B. gegen Herpes simplex, das Acyclovir oder gegen Krankheiten, die durch Rhinoviren verursacht werden, das Enviroxime, 4,6-Dichlorflavan, Chalcone RO 09-0410 (siehe British Medical Bulletin, Vol. 41, 386—390 (1985) oder Disoxavil (siehe Science, Vol. 233, 1286—1293 (1986)). Weiterhin wurde in der deutschen Patentanmeldung P 38 19 037 bereits vorgeschlagen, 2,4-disubstituierte Oxazol-Derivate zur Bekämpfung von Rhinoviruserkrankungen einzusetzen.

Überraschenderweise wurde nun gefunden, daß sich bestimmte Isoxazol-Derivate zur Behandlung bzw. zur Prophylaxe von Viruserkrankungen eignen.

Zum Erfindungsgegenstand gehören demzufolge Isoxazol-Derivate der Formel I



in der

A eine verzweigte oder unverzweigte Alkylengruppe mit 2 bis 12 C-Atomen,
 B eine verzweigte oder unverzweigte Alkylengruppe mit 1 bis 4 C-Atomen,
 R¹ Wasserstoff, C₁—C₆-Alkyl oder C₁—C₄-Alkoxy,
 R² und/oder R³ Wasserstoff, F, Cl, Br, J, Trifluormethyl, C₁—C₄-Alkyl oder C₁—C₄-Alkoxy und
 R⁴ Wasserstoff, C₁—C₄-Alkyl, C₁—C₄-Alkoxy oder einen aromatischen Kohlenwasserstoffrest mit bis zu 16 C-Atomen, der auch mit F, Cl, Br, J, Trifluormethyl, C₁—C₄-Alkyl oder C₁—C₄-Alkoxy bis zu dreifach substituiert sein kann,
 bedeuten, sowie deren physiologisch verträgliche Salze.

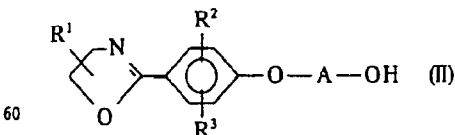
Bevorzugt sind Isoxazol-Derivate der Formel I, die dadurch gekennzeichnet sind, daß sie mindestens eines der nachfolgenden Merkmale aufweisen:

A ist eine verzweigte oder unverzweigte Alkylenkette mit 2 bis 6 C-Atomen,
 B ist eine Methyl- oder Ethylengruppe,
 R¹ ist eine C₁—C₃-Alkylgruppe,
 R² und/oder R³ ist Wasserstoff, Cl oder C₁—C₃-Alkyl,
 R⁴ ist eine C₁—C₃-Alkylgruppe oder ein Phenylrest, der mit bis zu drei C₁—C₃-Alkylgruppen oder Chloratomen substituiert sein kann.

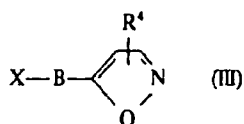
Besonders bevorzugt sind Isoxazol-Derivate der Formel I, die dadurch gekennzeichnet sind, daß sie mindestens eines der folgenden Merkmale aufweisen:

A ist eine unverzweigte Alkylenkette mit 2 bis 6 C-Atomen,
 B ist eine Methylengruppe,
 R¹ ist eine C₁—C₃-Alkylgruppe in 4-Stellung,
 R² und/oder R³ ist Wasserstoff oder Cl in 2- bzw. 6-Stellung,
 R⁴ ist eine C₁—C₃-Alkylgruppe in 3-Stellung oder eine Phenylgruppe, die in p-Stellung mit einer Methylgruppe substituiert sein kann.

Weiterhin gehört zum Erfindungsgegenstand ein Verfahren zur Herstellung von Verbindungen der Formel I, das dadurch gekennzeichnet ist, daß man eine Verbindung der Formel II



in der die Substituenten die zur Formel I genannten Bedeutungen haben, mit einer Verbindung der Formel III



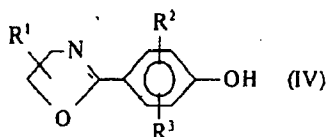
5

in der X F, Cl, Br oder J ist und R⁴ und B die zu Formel I genannten Bedeutungen haben, umgesetzt.

Die Umsetzung zur Herstellung der erfindungsgemäßen Verbindungen wird zweckmäßig mit äquimolaren Mengen der jeweiligen Ausgangsstoffe (Verbindungen der Formeln II und III) durchgeführt, vorteilhaft in einem polaren aprotischen Lösungsmittel wie z. B. Aceton, Ethylmethylketon, Tetrahydrofuran, 1,2-Dimethoxyethan, 1,4-Dioxan, Acetonitril, Dimethylformamid, Dimethylsulfoxid. Um die bei der Reaktion entstehenden Halogenwasserstoffe zu neutralisieren, werden vorzugsweise Basen wie z. B. Natriumhydrid, Lithiumhydrid, Kaliumcarbonat, Natriumhydrogencarbonat, Triethylamin oder Pyridin zugesetzt.

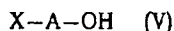
Die nach dem beschriebenen Verfahren hergestellten Verbindungen der allgemeinen Formel I sind als basische Substanzen zur Bildung von Salzen befähigt. Die Herstellung von pharmazeutischen akzeptablen Säureadditionssalzen von Verbindungen der Formel I erfolgt nach allgemein üblichen und jedem Fachmann geläufigen Methoden. Für die Verbindungen der Formel I kommen sowohl Salze mit anorganischen als auch Salze mit organischen Säuren in Betracht, beispielsweise Hydrochloride, Hydrobromide, Sulfate, Methansulfonate, p-Toluolsulfonate, Fumarate, Tartrate, Citrate, Maleinate, Ascorbate oder Acetate.

Die Verbindungen der Formel II werden vorzugsweise durch die Umsetzung von Phenolen der allgemeinen Formel IV



25

worin R¹, R² und R³ die zu Formel I angegebenen Bedeutungen haben, mit geeigneten ω-Halogenalkanolen der Formel V



35

worin X Fluor, Chlor, Brom oder Jod bedeutet und A die zu Formel I genannten Bedeutungen hat, hergestellt.

Die Verbindungen der Formel IV können nach in der Literatur beschriebenen Methoden hergestellt werden (siehe z. B. EP 2 07 454). Die Verbindungen der Formel V sind käuflich oder lassen sich nach allgemein bekannten Methoden herstellen. Die Verbindungen der Formel III können nach literaturbekannten Methoden hergestellt werden (siehe z. B. deutsche Offenlegungsschrift 25 49 962).

Ein weiteres Verfahren für die Synthese der Verbindungen der Formel I, das ebenfalls Gegenstand der vorliegenden Erfindung ist, wird in nachfolgendem Schema erläutert:

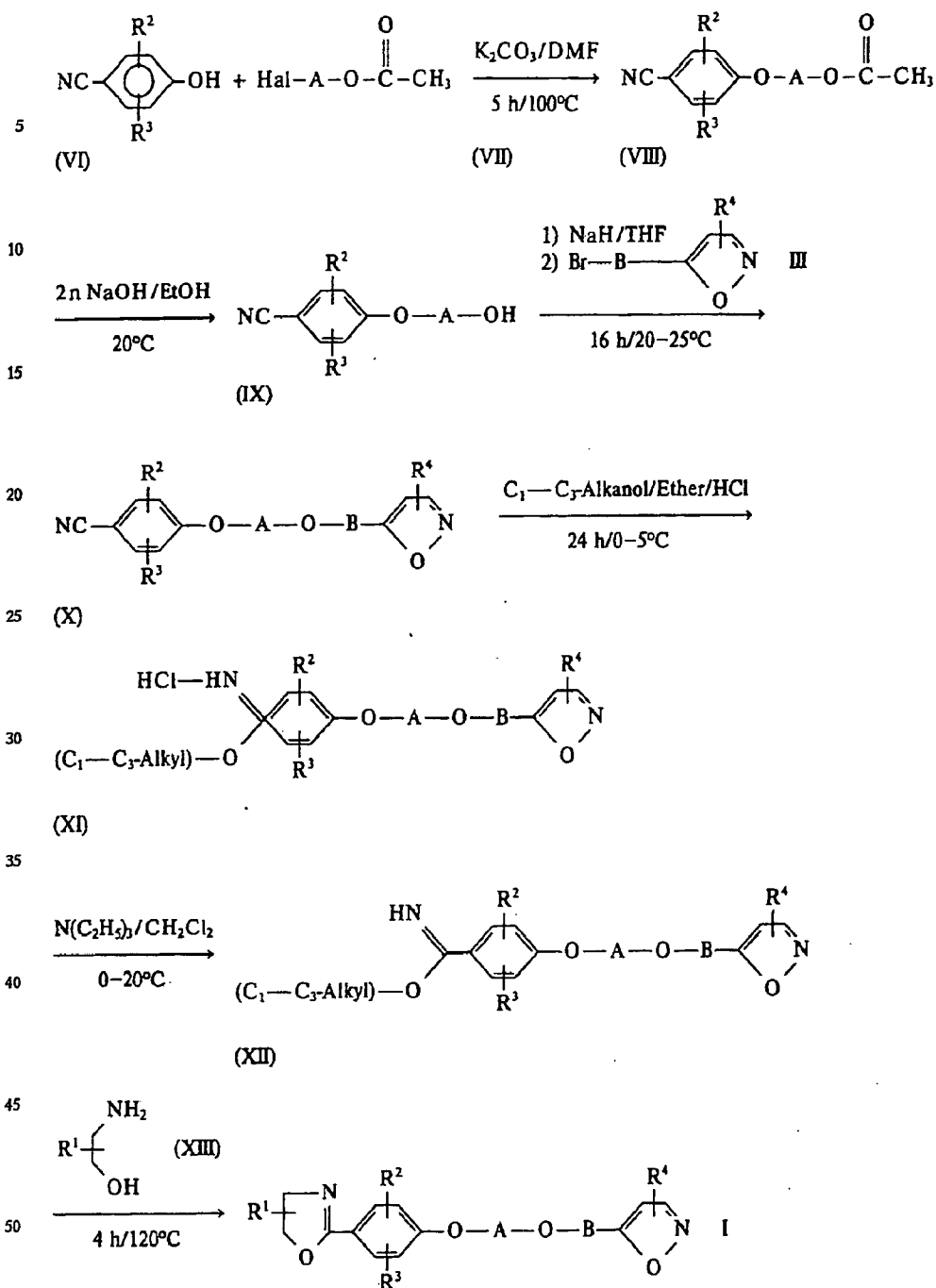
Die einzelnen Umsetzungen können unter unterschiedlichen Bedingungen ablaufen; die angegebenen Bedingungen und Reagenzien sind als beispielhaft anzusehen. Die in den Formeln angegebenen Substituenten R¹ bis R⁴ sowie A und B haben dieselbe Bedeutung, wie zu Formel I angegeben:

50

55

60

65



Das gegebenenfalls substituierte 4-Hydroxybenzonitril (VI) kann mit einem Essigsäurehalogenalkylester, vorzugsweise Essigsäurejodalkylester (VII), vorteilhaft in einem polar aprotischen Lösungsmittel, wie z. B. Dimethylformamid, in Gegenwart einer Base, wie z. B. K_2CO_3 in mehrstündiger Reaktion bei erhöhter Temperatur, vorzugsweise bei ca. 100°C , zu einer Verbindung der Formel VIII umgesetzt werden. Das erhaltene Produkt läßt sich hydrolysieren durch Versetzen mit einer wäßrigen Base, z. B. 2 n NaOH unter Zusatz von Alkohol, vorzugsweise Ethanol, zu Verbindungen der Formel IX.

Die Verbindung der Formel IX kann durch Umsetzen mit

1. Alkalihydrid, vorzugsweise Natriumhydrid, in geeignetem inerten Lösungsmittel, z. B. Tetrahydrofuran und
2. einer Verbindung der Formel III, vorzugsweise bei Raumtemperatur, in eine Verbindung der Formel X

umgewandelt werden. Die Verbindungen der Formel X sind neu und ebenfalls Gegenstand der vorliegenden Erfindung. Das erhaltene Produkt läßt sich durch Versetzen mit einem Alkohol mit 1 bis 3 C-Atomen, vorzugs-

weise Methanol, in Gegenwart eines aprotischen Lösungsmittels, vorzugsweise Dialkylether, und einem Halogenwasserstoff, vorzugsweise HCl, zweckmäßigerweise bei Temperaturen im Bereich von 0°C, zu den neuen Verbindungen der Formel XI umsetzen. Das entstandene Produkt läßt sich anschließend z. B. mit einem Trialkylamin, vorzugsweise Triethylamin in einem inerten Lösungsmittel, vorzugsweise Methylenchlorid bei Temperaturen von zweckmäßigerweise ca. 0 bis 20°C, zu der Verbindung der Formel XII umsetzen, die ebenfalls Gegenstand der vorliegenden Erfindung ist. Das Zielprodukt der Formel I läßt sich aus der Verbindung der Formel XII durch Umsetzen mit der Verbindung der Formel XIII, in der der Substituent R¹ in 2- oder 3-Stellung gebunden sein kann, bei erhöhter Temperatur, vorzugsweise bei ca. 120°C, erhalten.

Die Verbindungen der Formel VI sind entweder bekannt oder werden aus den entsprechenden 4-Hydroxybenzonitril durch Halogenierung oder Alkylierung nach an sich bekannten Methoden hergestellt. Die Verbindungen der Formel VII werden nach literaturbekannten Methoden (z. B. Tetrahedron Letters 23, 681—684 (1982)) hergestellt.

Die Verbindungen der Formel I besitzen wertvolle pharmakologische Eigenschaften, insbesondere eine antivirale Wirkung, vor allem gegen Picornaviren. Die erfindungsgemäßen Verbindungen sind gegen verschiedene Picornaviren wirksam und eignen sich daher zur Bekämpfung von Infektionen mit Picornaviren und unterschiedlicher, durch Viren verursachter Krankheiten, wie z. B. Erkrankungen des oberen Respirationstraktes, Endokarditis oder Erkrankungen des Darms sowohl bei Menschen als auch bei Tieren. Besondere Bedeutung haben die erfindungsgemäßen Verbindungen bei der Bekämpfung von Infektionen mit Rhinoviren und von Erkrankungen, die durch Infektion mit Rhinoviren verursacht worden sind.

Die Erfindung betrifft daher weiter die Anwendung der erfindungsgemäßen Verbindungen, insbesondere bei der Behandlung und Prophylaxe von Erkrankungen des oberen Respirationstraktes, Endokarditis oder Erkrankungen des Darms.

Die erfindungsgemäßen Verbindungen können entweder allein oder mit physiologisch verträglichen Hilfs- und/oder Trägerstoffen vermischt als Arzneimittel angewandt werden. Sie können zu diesem Zweck oral in Dosen von 0,1—10 mg/kg/Tag, vorzugsweise 0,2—8 mg/kg/Tag oder parenteral (z. B. intravenös, subcutan oder intramuskulär) in Dosen von 0,05—5 mg/kg/Tag, vorzugsweise 0,1—2 mg/kg/Tag, rectal oder lokal (topisch) insbesondere als Aerosol appliziert werden. Sie werden zweckmäßig in Dosierungseinheiten verabreicht, die mindestens die wirksame Menge der erfindungsgemäßen Verbindungen, bevorzugt 30—300 mg, besonders bevorzugt 50—250 mg enthalten. Diese Werte beziehen sich auf einen erwachsenen Menschen mit einem Gewicht von 75 kg. Die Dosierung kann in schweren Fällen auch erhöht werden. In vielen Fällen genügen jedoch auch geringere Dosen.

Die erfindungsgemäßen Verbindungen können auch in Kombination mit anderen Wirkstoffen, insbesondere Antivirumitteln und Immunstimulantien, wie z. B. Interferonen oder Interferon-Induktoren verabreicht werden.

Die Erfindung umfaßt weiterhin die Verwendung der erfindungsgemäßen Verbindungen bei der Herstellung von Arzneimitteln, die zur Behandlung und Prophylaxe der vorstehend genannten Krankheiten eingesetzt werden.

Ein weiterer Gegenstand der Erfindung sind Arzneimittel, die mindestens eine der erfindungsgemäßen Verbindungen der Formel I und/oder mindestens eines ihrer pharmakologisch verträglichen Salze enthalten.

Die Arzneimittel werden nach an sich bekannten, dem Fachmann geläufigen Verfahren hergestellt. Als Arzneimittel werden die erfindungsgemäßen pharmakologisch wirksamen Verbindungen (= Wirkstoff) entweder als solche oder vorzugsweise in Kombination mit geeigneten pharmazeutischen Hilfs- und/oder Trägerstoffen in Form von Tabletten, Dragees, Kapseln, Suppositorien, Emulsionen, Suspensionen oder Lösungen eingesetzt, wobei der Wirkstoffgehalt bis etwa 95%, vorteilhafterweise zwischen 10 und 75% beträgt.

Geeignete Hilfs- bzw. Trägerstoffe für die gewünschte Arzneimittelformulierung sind beispielsweise neben Lösemitteln, Gelbildner, Suppositoriengrundlagen, Tabletten-Hilfsstoffe und anderen Wirkstoffträgern auch Antioxidantien, Dispergiermittel, Emulgatoren, Entschäumer, Geschmackskorrigentien, Konservierungsmittel, Lösungsvermittler oder Farbstoffe.

Die Wirkstoffe können oral, intranasal, parenteral, intravenös oder rektal appliziert werden, wobei neben der oralen Applikation insbesondere die intranasale Applikation als Aerosol bevorzugt ist.

Für eine orale Anwendungsform werden die aktiven Verbindungen mit den dafür geeigneten Zusatzstoffen wie z. B. Trägerstoffen, Stabilisatoren oder inerten Verdünnungsmitteln vermischt und durch die üblichen Methoden in geeignete Darreichungsformen gebracht, wie Tabletten, Dragees, Stechkapseln, wäßrige oder ölige Lösungen. Als inerte Trägerstoffe können z. B. Gummi arabicum, Magnesia, Magnesiumcarbonat, Kaliumphosphat, Milchsüßholz, Glukose oder Stärke, insbesondere Maisstärke verwendet werden. Dabei kann die Zubereitung sowohl als Trocken- als auch als Feuchtgranulat erfolgen. Als ölige Trägerstoffe oder Lösemittel kommen beispielsweise pflanzliche oder tierische Öle in Betracht, wie z. B. Sonnenblumenöl oder Lebertran.

Zur subkutanen oder intravenösen Applikation werden die aktiven Verbindungen oder deren physiologisch verträgliche Salze, gewünschtenfalls mit den dafür geeigneten Substanzen wie Lösungsvermittler, Emulgatoren oder weiteren Hilfsstoffen in Lösung, Suspension oder Emulsion gebracht. Als Lösungsmittel kommen z. B. in Frage physiologische Kochsalzlösung oder Alkohole, z. B. Ethanol, Propanol, Glycerin, daneben auch Zuckerlösungen wie Glucose- oder Mannitlösungen, oder auch eine Mischung aus den verschiedenen genannten Lösungsmitteln.

Nachfolgend ist die Erfindung an Hand von Beispielen näher erläutert.

Beispiel 1

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxyethoxymethyl]-3-methyl-isoxazol

3,9 g (0,09 Mol) Natriumhydrid (55–60%) werden mit Petrolether gewaschen und in 10 ml THF (rein) vorgelegt, dazu eine Lösung von 18,6 g (0,09 Mol) 2-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-ethanol in 100 ml THF (rein) bei ca. 20°C getropft. Die Temperatur steigt dabei bis auf 42°C. Das Gemisch wird 20 Minuten unter Rückfluß gerührt, dann ohne zu heizen eine Lösung von 15,8 g (0,09 Mol) 5-Brommethyl-3-methyl-isoxazol in 15 ml THF (rein) gelöst langsam zugetropft. Durch die exotherme Reaktion steigt die Temperatur bis auf 68°C an. Nachträglich wird das Reaktionsgemisch 1 Stunde unter Rückfluß gerührt und über Nacht bei Raumtemperatur stehengelassen. Anschließend wird das Reaktionsgut in 500 ml Eiswasser gegeben, der ausgefallene Niederschlag abgesaugt und mit Wasser nachgewaschen. Nach dem Trocknen bei Raumtemperatur wird das Produkt aus Essigsäureethylester umkristallisiert. Ausbeute: 19 g, Schmp.: 98–101°C.

10

Beispiel 2

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxypropionoxymethyl]-3-methyl-isoxazol

15

Die Titelverbindung wird analog Beispiel 1 aus 3-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-propanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp. 70–74°C.

Beispiel 3

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxybutoxymethyl]-3-methyl-isoxazol

20

0,96 g (0,022 Mol) Natriumhydrid (55–60%) werden in 10 ml DMF (rein) suspendiert, dazu 4,7 g (0,02 Mol) 4-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-butanol in 60 ml DMF (rein) gelöst bei Raumtemperatur unter Rühren getropft. Es wird 20 Minuten bei 40°C, dann 30 Minuten bei 50–60°C gerührt. Zu diesem Gemisch wird dann eine Lösung von 3,52 g (0,02 Mol) 5-Brommethyl-3-methyl-isoxazol in 10 ml DMF (rein) getropft, anschließend wird 3 Stunden bei 70°C gerührt. Das Reaktionsgemisch wird abgekühlt, in 100 g Eiswasser gegeben und mit Ether extrahiert. Die organische Phase wird über MgSO₄ getrocknet und im Vakuum eingedampft. Der ölige Rückstand (4,4 g) wird über eine 120 g Kieselgel (Amicon-Grace, 70–200 µ)-Säule chromatographisch gereinigt (Laufmittel: Methylenchlorid/Methanol-Gemisch 9 : 1). Ausbeute: 2,0 g, Schmp.: 49–51°C.

30

Beispiel 4

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxypropyloxymethyl]-3-methyl-isoxazol

35

Die Titelverbindung wird analog Beispiel 3 aus 5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-pentanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 58–60°C.

Beispiel 5

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxyhexyloxymethyl]-3-methyl-isoxazol

40

Die Titelverbindung wird analog Beispiel 3 aus 6-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-hexanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 68–72°C.

45

Beispiel 6

5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxyethoxymethyl]-3-methyl-isoxazol

50

1,1 g (0,024 Mol) Natriumhydrid (55–60%) werden mit Petrolether gewaschen und in 10 ml THF (rein) unter Argon suspendiert. Dazu wird eine Lösung von 4,8 g (0,02 Mol) 2-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-ethanol in 40 ml THF (rein) unter Rühren getropft und das Reaktionsgemisch 30 Minuten unter Rückfluß gerührt. Zu diesem Gemisch wird dann eine Lösung von 4,5 g (0,024 Mol) 5-Brommethyl-3-methyl-isoxazol in 10 ml THF (rein) getropft und 4 Stunden unter Rückfluß gerührt. Das Reaktionsgut wird dann im Vakuum eingedampft, der Rückstand in Eiswasser verrührt und der Niederschlag abgesaugt. Das so erhaltene Produkt wird über 80 g Kieselgel (Amicon-Grace, 70–200 µ)-Säule gereinigt (Laufmittel: Methylenchlorid/Essigsäureethylester-Gemisch 1 : 1). Das Produkt wird aus Methanol umkristallisiert. Ausbeute: 4,4 g, Schmp.: 96–98°C.

55

Beispiel 7

5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxypropoxymethyl]-3-methyl-isoxazol

60

Die Titelverbindung wird analog Beispiel 6 aus 3-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-propanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 98–101°C.

65

Beispiel 8

5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxybutoxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 6 aus 4-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-butanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 77–80°C.

Beispiel 9

5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]pentylloxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 6 aus 5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-pentanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 89–91°C.

Beispiel 10

5-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]hexylloxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 6 aus 6-[2-Chlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-hexanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 46–48°C.

Beispiel 11

5-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]propoxymethyl]-3-methyl-isoxazol

2,9 g (0,01 Mol) 3-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-propanol und 3,62 g (0,02 Mol) 5-Brommethyl-3-methyl-isoxazol werden in 40 ml reinem THF vorgelegt und unter Rühren werden bei 15–20°C 0,52 g (0,012 Mol) Natriumhydrid (55–60%) portionsweise eingetragen. Es wird 24 Stunden bei ca. 20°C gerührt und dann vorsichtig in 100 g Eiswasser gegeben. Das Gemisch wird mit Methylenchlorid extrahiert, die organische Phase mit gesättigter NaCl-Lösung gewaschen, über MgSO₄ getrocknet und im Vakuum eingedampft. Der Rückstand wird über 200 g Kieselgel (Amicon-Grace, 70–200 µ)-Säule chromatographiert (eluiert zunächst mit Methylenchlorid und anschließend mit Methylenchlorid/Methanol-Gemisch 99 : 1). Nach Eindampfen des Lösungsmittels im Vakuum bleibt die Substanz als reines Festprodukt zurück. Ausbeute: 1,05 g, Schmp.: 60–64°C.

Beispiel 12

5-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]butoxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 11 aus 4-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-butanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Schmp.: 67–71°C.

Beispiel 13

5-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]pentylloxymethyl]-3-methyl-isoxazol

1,1 g (0,024 Mol) Natriumhydrid (55–60%) werden unter Argonatmosphäre mit Pentan gewaschen und in 10 ml reinem Dimethoxyethan suspendiert. Dazu werden bei ca. 25°C eine Lösung von 6,4 g (0,02 Mol) 5-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-pentanol in 30 ml Dimethoxymethan getropft. Die Suspension wird 1 Stunde bei 50–60°C gerührt, eine Lösung von 4,4 g (0,024 Mol) 5-Brommethyl-3-methyl-isoxazol in 10 ml Dimethoxyethan werden tropfenweise zugegeben und es wird 5 Stunden unter Rückfluß gerührt. Anschließend wird das Lösungsmittel im Vakuum eingedampft, der feste Rückstand mit Eiswasser versetzt und mit Methylenchlorid extrahiert. Nach Eindampfen des Lösungsmittels wird der Rückstand mit Ether verrührt, vom ungelösten Produkt abfiltriert und das Filtrat wieder eingedampft. Der so erhaltene Rückstand wird über 80 g Kieselgel (Amicon-Grace, 70–200 µ)-Säule chromatographiert (Laufmittel: Essigester-Cyclohexan-Gemisch 6 : 4). Schmp.: 39–41°C.

Beispiel 14

5-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]hexylloxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 13 aus 6-[2,6-Dichlor-4-(4,5-dihydro-2-oxazolyl)-phenoxy]-hexanol und 5-Brommethyl-3-methyl-isoxazol hergestellt. Das Produkt ist ölig.

Beispiel 15

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]ethoxymethyl]-3-(4-tolyl)-isoxazol

0,44 g (0,01 Mol) Natriumhydrid (55–60%) werden mit Petrolether gewaschen und in 10 ml THF (rein) suspendiert. Dazu werden unter Rühren eine Lösung von 2,07 g (0,01 Mol) 2-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-ethanol in 40 ml THF (rein) getropft und das Gemisch 20 Minuten bei 60°C gerührt. Das Reaktionsgemisch wird dann auf 20°C abgekühlt und eine Lösung von 2,52 g (0,01 Mol) 5-Brommethyl-3-(4-tolyl)-isoxazol in 10 ml THF (rein) zugegetropft. Es wird weitere 3 Stunden unter Rückfluß gekocht. Anschließend wird das Lösungs-

mittel im Vakuum eingedampft und der Rückstand in Eiswasser gegeben. Das ausgefallene Produkt wird abgesaugt und aus Methanol umkristallisiert. Ausbeute: 2,4 g, Schmp.: 118–121°C.

Beispiel 16

5

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxypropoxymethyl]-3-(4-tolyl)-isoxazol

Die Titelverbindung wird analog Beispiel 15 aus 3-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-propanol und 5-Brommethyl-3-(4-tolyl)-isoxazol hergestellt. Schmp.: 123–125°C.

10

Beispiel 17

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxybutoxymethyl]-3-(4-tolyl)-isoxazol

15 Die Titelverbindung wird analog Beispiel 15 aus 4-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-butanol und 5-Brommethyl-3-(4-tolyl)-isoxazol hergestellt. Schmp.: 83–85°C.

Beispiel 18

20

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy-pentyloxymethyl]-3-(4-tolyl)-isoxazol

Die Titelverbindung wird analog Beispiel 15 aus 5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-pentanol und 5-Brommethyl-3-(4-tolyl)-isoxazol hergestellt. Schmp.: 113–115°C.

25

Beispiel 19

5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxyhexyloxymethyl]-3-(4-tolyl)-isoxazol

Die Titelverbindung wird analog Beispiel 15 aus 6-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-hexanol und 5-Brommethyl-3-(4-tolyl)-isoxazol hergestellt. Schmp.: 88–92°C.

30

Beispiel 20

3-(4-Chlorphenyl)-5-[4-(4,5-dihydro-2-oxazolyl)-phenoxyethoxymethyl]-isoxazol

35

Die Titelverbindung wird analog Beispiel 15 aus 2-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-ethanol und 5-Brommethyl-3-(4-chlorphenyl)-isoxazol hergestellt. Schmp.: 124–126°C.

Beispiel 21

40

3-(4-Chlorphenyl)-5-[4-(4,5-dihydro-2-oxazolyl)-phenoxypropoxymethyl]-isoxazol

Die Titelverbindung wird analog Beispiel 15 aus 3-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-propanol und 5-Brommethyl-3-(4-chlorphenyl)-isoxazol hergestellt. Schmp.: 120–122°C.

45

Beispiel 22

3-(4-Chlorphenyl)-5-[4-(4,5-dihydro-2-oxazolyl)-phenoxybutoxymethyl]-isoxazol

50 Die Titelverbindung wird analog Beispiel 15 aus 4-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-butanol und 5-Brommethyl-3-(4-chlorphenyl)-isoxazol hergestellt. Schmp.: 89–91°C.

Beispiel 23

55

3-(4-Chlorphenyl)-5-[4-(4,5-dihydro-2-oxazolyl)-phenoxy-pentyloxymethyl]-isoxazol

Die Titelverbindung wird analog Beispiel 15 aus 5-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-pentanol und 5-Brommethyl-3-(4-chlorphenyl)-isoxazol hergestellt. Schmp.: 117–120°C.

60

Beispiel 24

3-(4-Chlorphenyl)-5-[4-(4,5-dihydro-2-oxazolyl)-phenoxyhexyloxymethyl]-isoxazol

65 Die Titelverbindung wird analog Beispiel 15 aus 6-[4-(4,5-Dihydro-2-oxazolyl)-phenoxy]-hexanol und 5-Brommethyl-3-(4-chlorphenyl)-isoxazol hergestellt. Schmp.: 106–108°C.

Beispiel 25

5-[2-Chlor-4-(4,5-dihydro-4-ethyl-2-oxazolyl)-phenoxyethoxymethyl]-3-methyl-isoxazol

3,8 g (0,0117 Mol) 3-Chlor-4-(3-methyl-isoxazol-5-yl-methoxyethoxy)-benzimidomethylester und 1,04 g (0,0117 Mol) 2-Aminobutanol werden unter Feuchtigkeitsausschluß 4 Stunden auf 120°C (Badtemperatur) erhitzt, das entstandene Produkt (Öl) über eine 80 g Kieselgel (Amicon-Grace, 70–200 µ)-Säule chromatographiert (erst mit Methylenchlorid dann mit Methylenchlorid-Methanol-Gemisch 99 : 1 eluiert). Nach Eindampfen des Lösungsmittels werden 2,1 g von dem erwünschten Produkt rein erhalten. Das Produkt ist ölig.

Beispiel 26

5-[2-Chlor-4-(4,5-dihydro-4-ethyl-2-oxazolyl)-phenoxypropoxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 25 aus 3-Chlor-4-(3-methyl-isoxazol-5-yl-methoxypropoxy)-benzimidomethylester und 2-Aminobutanol hergestellt. Schmp.: 53–55°C.

Beispiel 27

5-[2-Chlor-4-(4,5-dihydro-4-ethyl-2-oxazolyl)-phenoxybutoxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 25 aus 3-Chlor-4-(3-methyl-isoxazol-5-yl-methoxybutoxy)-benzimidomethylester und 2-Aminobutanol hergestellt. Das Produkt ist ölig.

Beispiel 28

5-[2-Chlor-4-(4,5-dihydro-4-ethyl-2-oxazolyl)-phenoxy-pentyloxymethyl]-3-methyl-isoxazol

Die Titelverbindung wird analog Beispiel 25 aus 3-Chlor-4-(3-methyl-isoxazol-5-yl-methoxy-pentyloxy)-benzimidomethylester und 2-Aminobutanol hergestellt. Das Produkt ist ölig.

Pharmakologische Beispiele

Antivirale Wirksamkeit

Die antivirale Wirkung der erfindungsgemäßen Verbindungen wurde in in-vitro Versuchen geprüft. Dazu wurden die erfindungsgemäßen Verbindungen in verschiedenen Verdünnungen zu Zellkulturen von Hela-Zellen in Mikrotiterplatten gegeben. Nach 3 Stunden wurden die Kulturen mit verschiedenen humanpathogenen Rhinoviren und anderen Picornaviren infiziert. 48–72 Stunden nach der Infektion wurde der Therapieerfolg anhand des cytopathogenen Effektes mikroskopisch und nach Neutralrot-aufnahmen (Farbtest nach Finter) photometrisch bestimmt (Finter, N. B., in "Interferones" (N. B. Finter et al), North Holland Publishing Co., Amsterdam (1966)). Die minimale Konzentration, bei der etwa die Hälfte der infizierten Zellen keinen cytopathogenen Effekt zeigen, wird als minimale Hemmkonzentration (MHK) betrachtet. Die Ergebnisse sind in der Tabelle I zusammengefaßt.

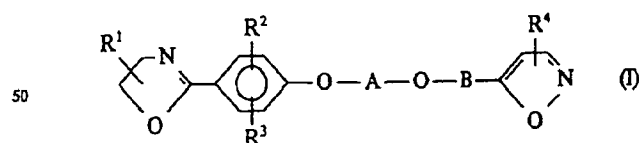
Tabelle I

5	Substanz aus Beispiel	MHK (µg/ml)		HRV 11	Polio-V Typ I	Coxsackie		DTM (µg/ml)
		HRV 2	HRV 3			A 15	B 4	
10	2	133,3	0,18	14,8	133,3	14,8	—	133,3
	4	44,4	4,94	44,4	—	4,94	—	133,3
	5	14,8	1,65	14,8	—	14,8	—	133,3
	7	0,55	0,18	0,55	—	4,44	14,8	133,3
15	8	0,55	0,55	0,55	—	4,94	4,94	133,3
	9	0,55	1,65	0,55	—	4,94	4,94	≥400,0
	10	14,8	44,4	4,94	—	133,3	133,3	133,3
	11	0,18	1,65	1,65	400,0	133,3	44,4	≥400,0
20	12	0,18	0,55	0,55	—	44,4	14,8	133,3
	13	1,65	44,4	4,94	—	133,3	133,3	≥400,0
	14	0,18	14,8	0,55	—	44,4	44,4	133,3
	15	—	0,18	—	—	4,94	400,0	≥400,0
25	16	—	0,18	—	—	133,3	400,0	≥400,0
	17	—	4,94	—	400,0	44,4	—	≥400,0
	18	—	14,8	—	—	133,3	—	≥400,0
	19	—	44,4	—	—	44,4	—	≥400,0
30	20	—	0,18	—	—	14,8	400,0	≥400,0
	21	—	1,65	—	—	400,0	400,0	≥400,0
	23	—	44,4	—	—	400,0	—	≥400,0
	25	1,65	4,94	14,8	400,0	133,3	—	≥400,0
35	26	1,65	0,18	4,94	133,3	44,4	—	133,3
	27	14,8	44,4	4,94	—	—	400,0	≥400,0

— = unwirksam
 HRV = Human-Rhinovirus
 MHK = Minimale Hemmkonzentration
 DTM = Dosis tolerata maxima

Patentansprüche

1. Isoxazol-Derivate der Formel I



in denen

- 55 A eine verzweigte oder unverzweigte Alkylengruppe mit 2 bis 12 C-Atomen,
 B eine verzweigte oder unverzweigte Alkylengruppe mit 1 bis 4 C-Atomen,
 R¹ Wasserstoff, C₁–C₆-Alkyl oder C₁–C₄-Alkoxy,
 R² und/oder R³ Wasserstoff, F, Cl, Br, J, Trifluormethyl, C₁–C₄-Alkyl oder C₁–C₄-Alkoxy und
 60 R⁴ Wasserstoff, C₁–C₄-Alkyl, C₁–C₄-Alkoxy oder einen aromatischen Kohlenwasserstoffrest mit bis zu 16
 C-Atomen, der auch mit F, Cl, Br, J, Trifluormethyl, C₁–C₄-Alkyl oder C₁–C₄-Alkoxy bis zu dreifach
 substituiert sein kann,

bedeutet, sowie deren physiologisch verträgliche Salze.

- 65 2. Isoxazol-Derivate der Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß sie mindestens eines der
 nachfolgenden Merkmale aufweisen:

A ist eine verzweigte oder unverzweigte Alkylenkette mit 2–6 C-Atomen,

B ist eine Methylen- oder Ethylengruppe,
 R^1 ist eine C_1-C_3 -Alkylgruppe,
 R^2 und/oder R^3 ist Wasserstoff, Cl oder C_1-C_3 -Alkyl,
 R^4 ist eine C_1-C_3 -Alkylgruppe oder ein Phenylrest, der mit bis zu drei C_1-C_3 -Alkylgruppen oder Chloratomen substituiert sein kann.

5

3. Isoxazol-Derivate der Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß sie mindestens eines der folgenden Merkmale aufweisen:

A ist eine unverzweigte Alkylkette mit 2–6 C-Atomen, 10
 B ist eine Methylengruppe,
 R^1 ist eine C_1-C_3 -Alkylgruppe in 4-Stellung,
 R^2 und/oder R^3 ist Wasserstoff oder Cl in 2- bzw. 6-Stellung,
 R^4 ist eine C_1-C_3 -Alkylgruppe in 3-Stellung oder eine Phenylgruppe, die in p-Stellung mit einer Methylgruppe substituiert sein kann. 15

4. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel II



25

in der die Substituenten die in Anspruch 1 genannten Bedeutungen haben, mit einer Verbindung der Formel III



35

in der X F, Cl, Br oder J ist und R^4 und B die in Anspruch 1 genannten Bedeutungen haben, umsetzt.

5. Verfahren gemäß Anspruch 4, dadurch gekennzeichnet, daß man die Umsetzung in einem Lösungsmittel in Gegenwart einer Base durchführt.

6. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß mindestens eine der nachfolgenden Umsetzungen durchgeführt wird: 40

a) Umsetzung einer Verbindung der Formel VI



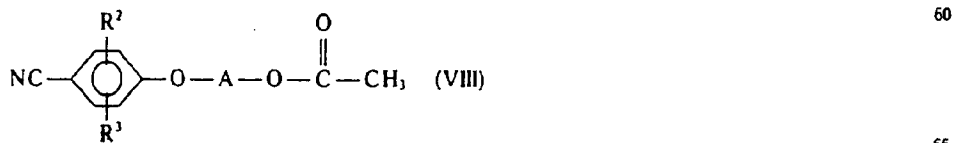
45

mit einer Verbindung der Formel VII



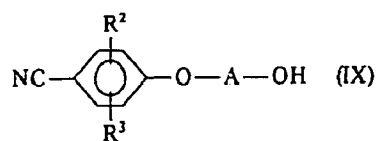
55

zu einer Verbindung der Formel VIII

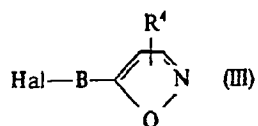


65

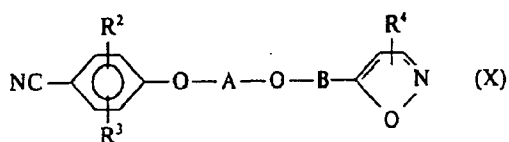
b) Hydrolyse der Verbindung der Formel VIII zur Verbindung der Formel IX



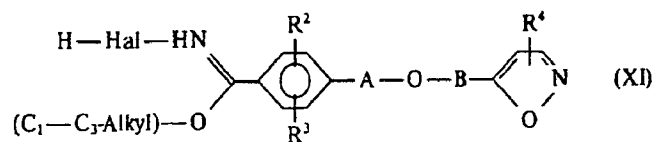
c) Umsetzung einer Verbindung der Formel IX mit einer Verbindung der Formel III



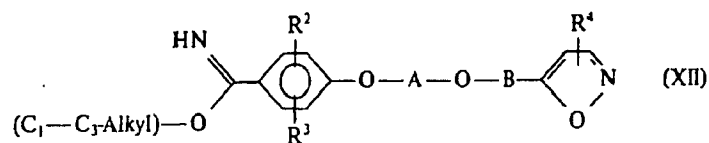
zu einer Verbindung der Formel X



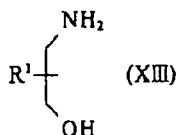
d) Umsetzung einer Verbindung der Formel X mit einem Alkohol zu einer Verbindung der Formel XI



e) Umsetzung einer Verbindung der Formel XI zu einer Verbindung der Formel XII

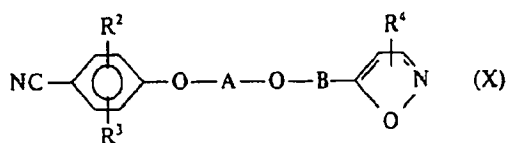


f) Umsetzung einer Verbindung der Formel XII mit einer Verbindung der Formel XIII



zu einer Verbindung der Formel I gemäß Anspruch 1,
wobei die Substituenten R^1 bis R^4 sowie A und B die zur Formel I in Anspruch 1 genannten Bedeutungen haben.

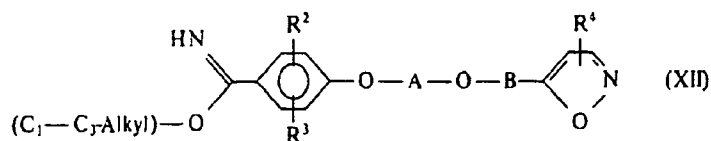
7. Verbindungen der Formel X



in der die Substituenten R^2 bis R^4 , A und B die in Anspruch 1 genannten Bedeutungen haben.

8. Verfahren zur Herstellung von Verbindungen der Formel X gemäß Anspruch 7, dadurch gekennzeichnet, daß die Umsetzung c) gemäß Anspruch 6 benutzt wird.

9. Verbindungen der Formel XII



in der die Substituenten R^2 bis R^4 sowie A und B die in Anspruch 1 genannten Bedeutungen haben, sowie deren Säureadditionssalze.

10. Verfahren zur Herstellung von Verbindungen der Formel XII, dadurch gekennzeichnet, daß die Umsetzungen d) und/oder e) gemäß Anspruch 6 benutzt werden.

11. Arzneimittel, dadurch gekennzeichnet, daß es mindestens eine Verbindung der Formel I gemäß Anspruch 1 und/oder mindestens eines ihrer physiologisch verträglichen Salze, gegebenenfalls neben anderen Hilfs- und/oder Trägerstoffen enthält.

12. Arzneimittel gemäß Anspruch 11, dadurch gekennzeichnet, daß es antiviral wirksame Mengen mindestens einer Verbindung gemäß Anspruch 1 und/oder mindestens eines ihrer physiologisch verträglichen Salze enthält.

13. Verwendung von Verbindungen der Formel I gemäß Anspruch 1 oder ihrer physiologisch verträglichen Salze zur Herstellung von Arzneimitteln.

14. Verwendung von Verbindungen der Formel I gemäß Anspruch 1 zur Bekämpfung oder Prophylaxe von Krankheiten, die durch Virusinfektion hervorgerufen sind.

15. Verwendung von Verbindungen der Formel I gemäß Anspruch 1 zur Bekämpfung oder Prophylaxe von Krankheiten, die durch Infektion mit Picornaviren hervorgerufen sind.

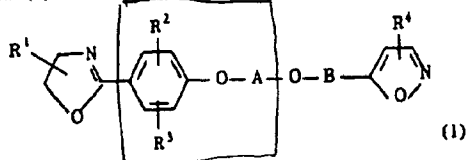
16. Verwendung von Verbindungen der Formel I gemäß Anspruch 1 zur Bekämpfung oder Prophylaxe von Krankheiten, die durch Infektion mit Rhinoviren hervorgerufen sind.

17. Verfahren zur Herstellung von Arzneimitteln, dadurch gekennzeichnet, daß mindestens eine Verbindung der Formel I oder mindestens eines ihrer physiologisch verträglichen Salze mit physiologisch verträglichen Hilfsstoffen und/oder Trägerstoffen in eine geeignete Darreichungsform gebracht wird.

★ reactant (IX)

90-037631/06 B03 FARM 25.07.88
HOECHST AG *DE 3825-170-A
23.07.88-DE-825170 (25.01.90) A61k-31/42 C07d-261/08
C07d-263/30 C07d-413/12
New isoxazol-5-yl-substd. 2-phenyl-2-oxazoline derivs. with
antiviral activity prep. e.g. by reaction of hydroxy-alkoxy-
phenyl-2-oxazolone(s) with 5-halo alkyl-isoxazole(s)
C90-016436

(A) Isoxazol-5-yl substd. 2-phenyl-2-oxazoline derivs. of
formula (I) and their salts are new:



A = opt. branched 2-12C alkylene;
B = opt. branched 1-4C alkylene;
R1 = H, 1-6C alkyl or 1-4C alkoxy;
R2, R3 = H, F, Cl, Br, I, CF3, 1-4C alkyl or 1-4C alkoxy;
R4 = H, 1-4C alkyl, 1-4C alkoxy, or an aromatic hydrocarbon

B(7-EI, 12-A6)

residue with up to 16 C-atoms opt. mono-, di- or tri-
substd. by F, Cl, Br, I, CF3, 1-4C alkyl or 1-4C
alkoxy.

(B) Also new and claimed are intermediates of formulae (X)
and (XII) (see "Preparation").

USE

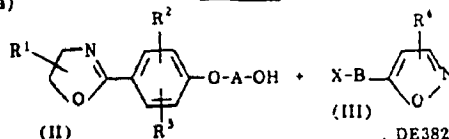
(1) have antiviral properties and can be used for the
prophylaxis of viral diseases.

Results of tests in cell cultures of HeLa cells infected
with various types of picorna and rhino viruses are given
in the specification.

PREPARATION

The following methods are claimed:

(a)

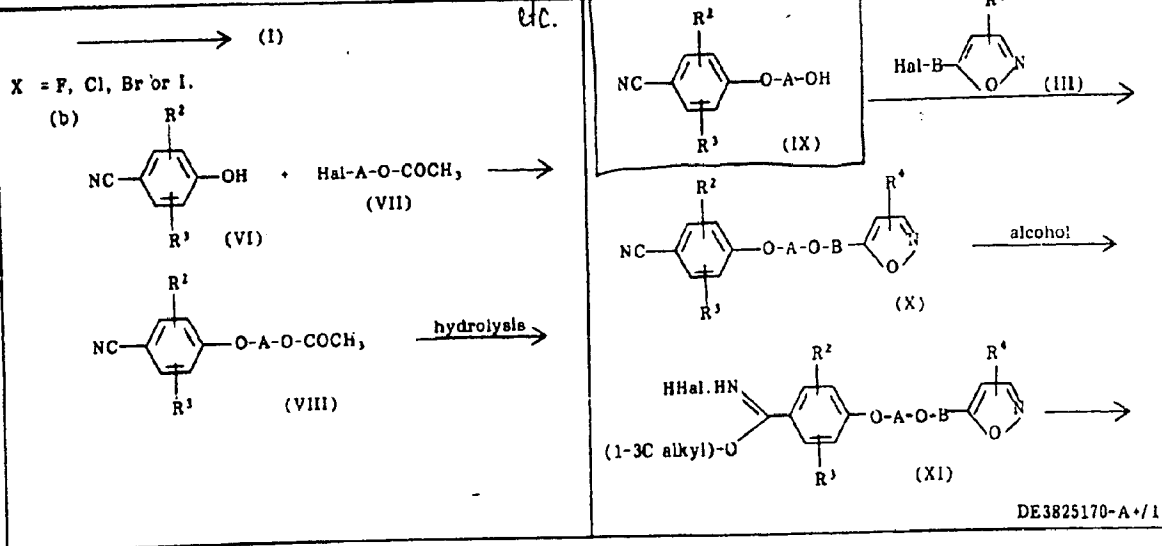


DE3825170-A*

R2, R3 = H, CF3

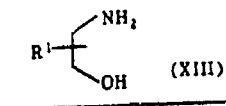
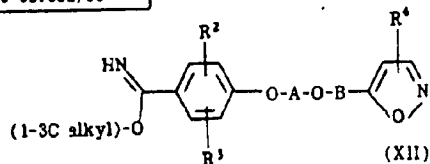
etc.

A = opt. branched alkylene



DE3825170-A*/1

90-037631/06



EXAMPLE

55-60% NaH (3.9g) is washed with petroleum ether,
suspended in pure THF (10 ml), treated dropwise at 20°C
with 2-[4-(4,5-dihydro-2-oxazolyl)phenoxy]ethanol (18.8g)
in pure THF (100 ml) (temp. rises to 42°C), stirred 20 mins.
at reflux, and slowly treated dropwise without heating with
a soln. of 5-bromomethyl-3-methyl-isoxazole (15.8g) in pure

THF (15 ml) (temp. rises to 68°C).

The mixt. is stirred 1 hr. at reflux,
let stand overnight at room temp., and added to ice-water
(500 ml). The prod. is filtered off, washed with water,
dried at room temp., and recrystd. from ethyl acetate to
give 5-[4-(4,5-dihydro-2-oxazolyl)phenoxyethoxymethyl]-3-
methyl-isoxazole (19g), m.pt. 98-101°C.
(13pp280HDDwgNo0/0).

DE3825170-A/2

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

(19) FEDERAL REPUBLIC OF GERMANY
 (12) GERMAN PATENT OFFICE
 (11) PATENT NO: 38 25 170 A1 (Offenlegungsschrift)

(51) Int. Cl.⁵: C 07 D 413/12
 C 07 D 261/08
 C 07 D 261/12
 A 61 K 31/42
 //C07D 413/12,
 261:06, 263:30

(21) Application No: P 38 25 170.1

(22) Application Date: July 23, 1988

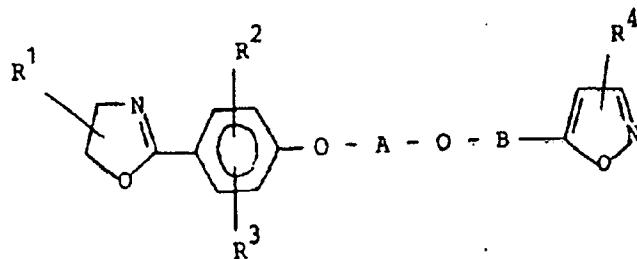
(43) Inspection Date: January 25, 1990

(71) Applicant: Hoechst AG, 6230 Frankfurt (Germany)

(72) Inventors: Akhileswar Sinharay, 6000 Frankfurt; Irvin Winkler,
 6237 Liederbach; Matthias Helsberg, 6233 Kelkeim
 (Germany)

(54) Substituted 5-[4-(4,5-dihydro-2-oxazolyl)phenoxyalkylenoxyalkyl] isoxazoles, [production] method, 5-(phenoxyalkylenoxyalkyl)isoxazoles as intermediate products for their production, and their use for the treatment of diseases caused by infection with viruses

New isoxazole derivatives of the following formula:



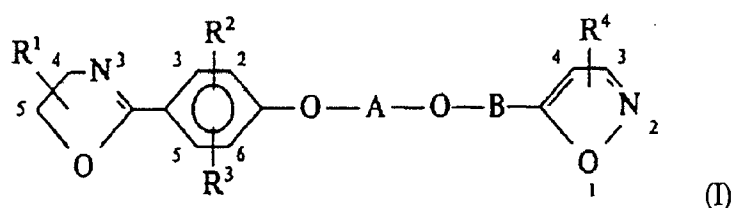
in which the substituents R^1 to R^4 and A and B have the aforementioned meanings, are suitable for the treatment of diseases caused by infection with viruses, in particular with picornaviruses.

Description

The treatment of viral infections or diseases caused by them (viral disease) with chemotherapeutic agents is important, because many viral diseases cannot be prevented with an inoculation, since the pertinent virus types frequently change their shell. Against numerous viral diseases, chemotherapeutics have already been described: for example, against Herpes simplex, acyclovir, or against diseases caused by rhinoviruses, enviroxime, 4,6-dichloroflavan, chalcone RO 09-0410 (see British Medical Bulletin, Vol. 41, 386-390 (1985), or disoxavil [sic; probably "disoxaril"] (see Science, Vol. 233, 1286-1293 (1986)). Furthermore, German Patent Application P 38 19 037 has already proposed using 2,4-disubstituted oxazole derivatives to treat diseases caused by rhinoviruses.

Surprisingly, it was then discovered that certain isoxazole derivatives are suitable for the treatment or for the prophylaxis of viral diseases.

Accordingly, isoxazole derivatives of formula I are the subject of the invention:



in which

A denotes a branched or unbranched alkylene group with 2 to 12 C atoms;

B, a branched or unbranched alkylene group with 1 to 4 C atoms;

R¹, hydrogen, C₁-C₆-alkyl, or C₁-C₄-alkoxy;

R² and/or R³, hydrogen, F, Cl, Br, I, trifluoromethyl, C₁-C₆-alkyl, or C₁-C₄-alkoxy; and

R⁴, hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, or an aromatic hydrocarbon radical with up to 16 C atoms, which can also be substituted, up to three times, with F, Cl, Br, I, trifluoromethyl, C₁-C₄-alkyl, or C₁-C₄-alkoxy;

and their physiologically acceptable salts.

Preferred are isoxazole derivatives of formula I, which are characterized in that they have at least one of the following features:

A is a branched or unbranched alkylene chain with 2 to 6 C atoms;

B is a methylene or ethylene group;

R¹ is a C₁-C₃-alkyl group;

R^2 and/or R^3 is hydrogen, Cl, or C_1 - C_3 -alkyl;

R^4 is a C_1 - C_3 -alkyl group or a phenyl radical, which can be substituted with up to three C_1 - C_3 -alkyl groups containing chlorine atoms.

Particularly preferred are isoxazole derivatives of formula I, which are characterized in that they have at least one of the following features:

A is an unbranched alkylene chain with 2 to 6 C atoms;

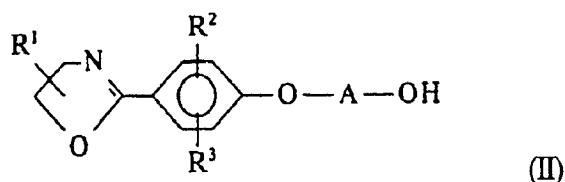
B is a methylene group;

R^1 is a C_1 - C_3 -alkyl group in the 4 position;

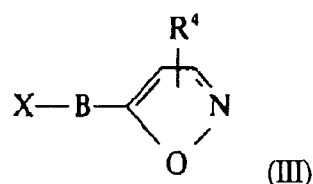
R^2 and/or R^3 is hydrogen or Cl in the 2 or 6 position;

R^4 is a C_1 - C_3 -alkyl group in the 3 position or a phenyl group, which can be substituted in the p position with a methyl group.

Furthermore, belonging to the subject of the invention, there is also a method for the preparation of compounds of formula I, which is characterized in that a compound of formula II:



in which the substituents have the meanings mentioned for formula I, is reacted with a compound of formula III:



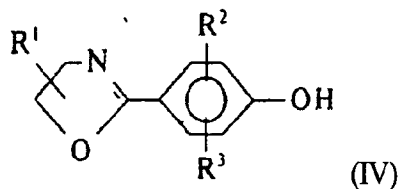
in which X is F, Cl, Br, or I, and R^4 and B have the meanings mentioned for formula I.

The reaction for the preparation of the compounds in accordance with the invention is appropriately carried out with equimolar quantities of the individual starting substances (compounds of formulas II and III), advantageously in a polar, aprotic solvent, such as acetone, ethyl methyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetonitrile, dimethylformamide, and dimethyl sulfoxide. In order to neutralize hydrogen halides formed during the reaction, bases such as sodium hydride, lithium hydride, potassium carbonate, sodium hydrogen carbonate, triethylamine, or pyridine are preferably added.

The compounds of general formula I, prepared according to the described method, are able to

form salts as basic substances. The preparation of pharmaceutically acceptable acid-addition salts of compounds of formula I takes place according to generally common methods that an expert is aware of. For the compounds of formula I, one can take into consideration salts with inorganic acids as well as salts with organic acids, for example, hydrochlorides, hydrobromides, sulfates, methanesulfonates, p-toluenesulfonates, fumarates, tartrates, citrates, maleinates, ascorbates, or acetates.

The compounds of formula II are preferably prepared by the reaction of phenols of general formula IV:



wherein R^1 , R^2 , and R^3 have the meanings indicated for formula I, with suitable ω -halogen alkanols of formula V:

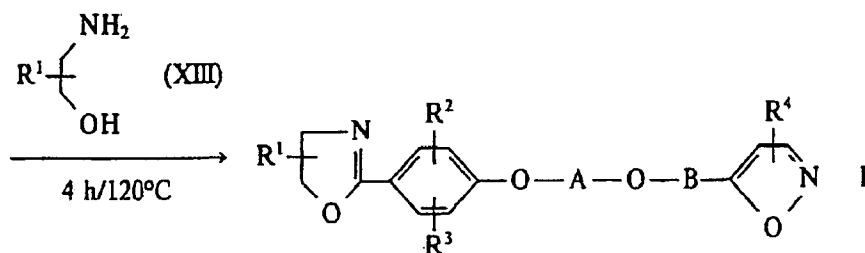
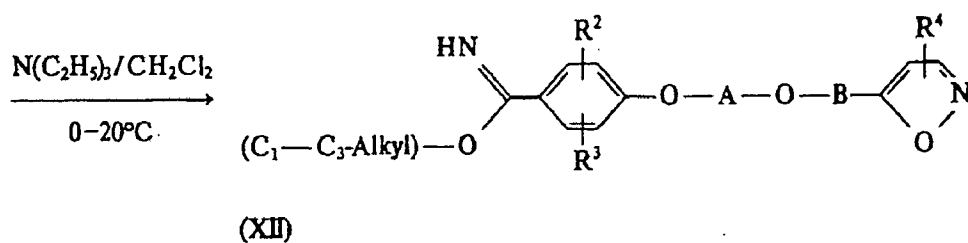
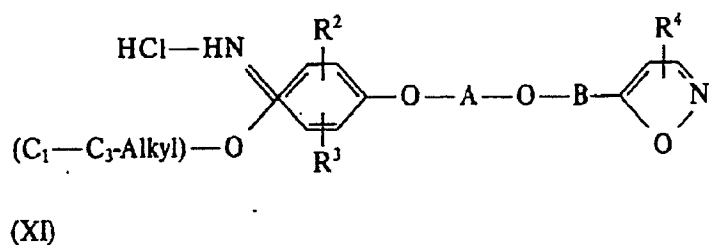
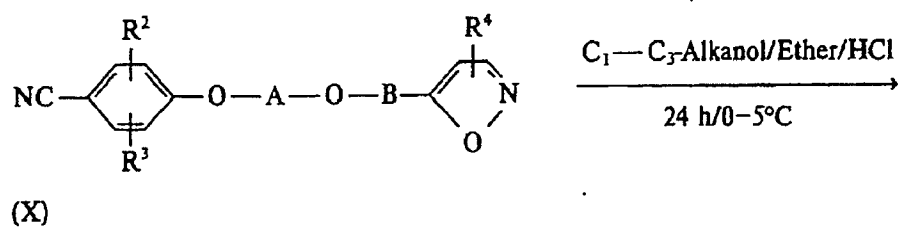
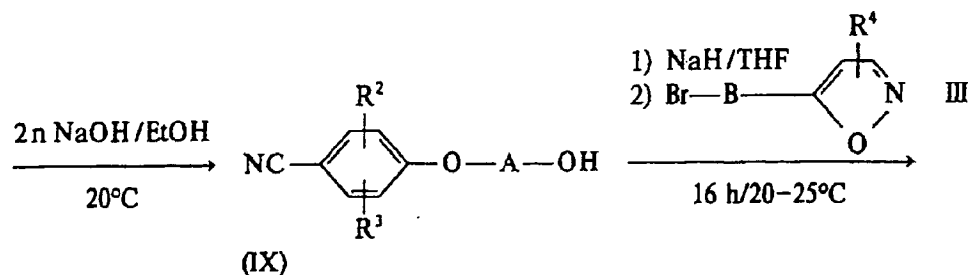
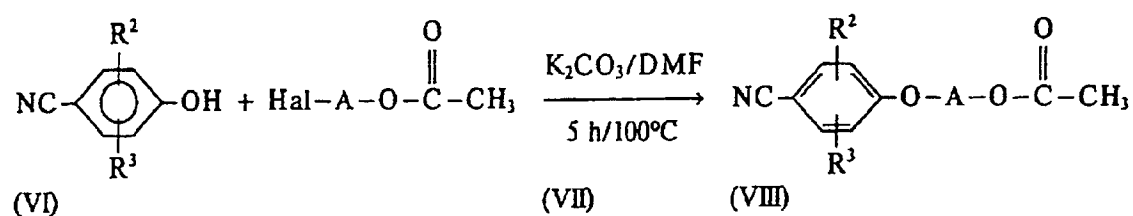


wherein X denotes fluorine, chlorine, bromine, or iodine, and A has the meanings mentioned for formula I.

The compounds of formula IV can be prepared according to methods described in the literature (see, for example, EP 2 07 454). The compounds of formula IV can be purchased or can be prepared according to generally known methods. The compounds of formula III can be prepared according to methods known from the literature (see, for example, German Patent No. 2,549,962 (Offenlegungsschrift)).

Another method for the synthesis of compounds of formula I, which also explains the subject of the invention under consideration, is explained in the following scheme:

The individual reactions can take place under various conditions; the indicated conditions and reagents are to be regarded as examples. The substituents indicated in the formulas -- R^1 to R^4 , A, and B -- have the same meaning as indicated for formula I:



The optionally substituted 4-hydroxybenzonitrile (VI) can be reacted with an acetic acid

halogen alkanyl ester, preferably acetic acid iodoalkanyl ester (VII), advantageously in a polar aprotic solvent such as dimethylformamide, in the presence of a base such as K_2CO_3 in a reaction at an elevated temperature, preferably up to approximately $100^\circ C$, lasting several hours, to form a compound of formula VIII. The product obtained can be hydrolyzed by reacting with an aqueous base, for example, 2N NaOH, with the addition of an alcohol, preferably ethanol, to form compounds of formula IX.

The compound of formula IX can be converted into a compound of formula X by reacting with

1. an alkali hydride, preferably sodium hydride, in a suitable inert solvent, for example, tetrahydrofuran; and
2. a compound of formula III, preferably at room temperature.

The compounds of formula X are new and also the subject of the invention under consideration. The products obtained can be reacted by mixing with an alcohol having 1 to 3 C atoms, preferably methanol, in the presence of an aprotic solvent, preferably a dialkyl ether, and a hydrogen halide, preferably HCl, appropriately at temperatures around $0^\circ C$ to form the new compounds of formula XI.

The product formed can be subsequently reacted, for example, with a trialkylamine, preferably triethylamine, in an inert solvent, preferably methylene chloride, at temperatures of, appropriately, approximately 0 to $20^\circ C$, to form the compound of formula XII, which is also the subject of the invention under consideration. The target product of formula I can be obtained from the compound of formula XII by reacting with the compound of formula XIII, in which the substituent R^1 can be bound in the 2 or 3 position, at an elevated temperature, preferably at approximately $120^\circ C$.

The compounds of formula VI are either known or are prepared from the corresponding 4-hydroxybenzonitrile by halogenation or alkylation according to methods that are in fact known. The compounds of formula VII are prepared according to methods known from the literature (for example, Tetrahedron Letters 23, 681-684 (1982)).

The compounds of formula I have valuable pharmacological characteristics, in particular, an antiviral effect, above all, against picornaviruses. The compounds in accordance with the invention are effective against various picornaviruses and are therefore suitable for treating infections with picornaviruses and different diseases caused by viruses, such as diseases of the upper respiratory tract, endocarditis, or intestinal diseases, both in humans as well as in animals. The compounds in accordance with the invention are especially important in treating infections with rhinoviruses and diseases caused by infection with rhinoviruses.

Therefore, the invention also concerns the use of the compounds in accordance with the invention, in particular, in the treatment and prophylaxis of diseases of the upper respiratory tract, endocarditis, or intestinal diseases.

The compounds in accordance with the invention can be used as medicines, either alone or

mixed with physiologically acceptable auxiliaries and/or carrier substances. For this purpose, they can be applied orally, in doses of 0.1-10 mg/kg/day, preferably 0.2-8 mg/kg/day, or parenterally (for example, intravenously, subcutaneously, or intramuscularly), in doses of 0.05-5 mg/kg/day, preferably, 0.1-2 mg/kg/day, rectally, or locally (topically), in particular, as an aerosol. They are appropriately administered in dosage units that contain at least the effective quantity of the compounds of the invention, preferably 30-300 mg, and with particular preference 50-250 mg. These values refer to an adult person with a weight of 75 kg. The dosage can be increased in serious cases also. In many cases, however, smaller doses are also sufficient.

The compounds in accordance with the invention can also be administered in combination with other active substances, in particular, antiviral agents and immunity stimulants, such as interferons or interferon inducers.

The invention also comprises the use of the compounds in accordance with the invention in the preparation of medicines used for the treatment and prophylaxis of the aforementioned diseases.

Another subject of the invention refers to medicines that contain at least one of the invention compounds of formula I and/or at least one of their pharmacologically acceptable salts.

The medicines are prepared according to methods that are, in fact, known and familiar to the expert. As medicines, the pharmacologically effective compounds (= active substance), in accordance with the invention, are used either as such or preferably in combination with suitable pharmaceutical auxiliaries and/or carrier substances, in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions, or solutions, wherein the active-substance content is up to approximately 95%, advantageously between 10 and 75%.

Suitable auxiliaries or carrier substances for the desired medicine formulation are, for example--in addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries, and other active-substance carriers -- as well as antioxidants, dispersants, emulsifiers, defoamers, flavor-correcting agents, preservatives, solubilizers, or dyes.

The active substances can be applied orally, intranasally, parenterally, intravenously, or rectally, wherein, in addition to the oral application, in particular, the intranasal application is preferred as an aerosol.

For an oral application form, the active compounds are mixed with additives suitable for such a purpose, such as carrier substances, stabilizers, or inert diluents and, by the usual methods, are brought into suitable administration forms, such as tablets, dragees, suppositories, or aqueous or oily solutions. As inert carrier substances, one can use, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular cornstarch. The preparation can also be dry or moist granules. As oily carrier substances or solvents, one can take into consideration, for example, vegetable or animal oils, such as sunseed oil or liver oil.

For the subcutaneous or intravenous application, the active compounds or their

physiologically acceptable salts are brought into solution, suspension, or emulsion, if desired, with substances suitable for such a purpose, such as solubilizers, emulsifiers, or other auxiliaries. As solvents, one can take into consideration, for example, common physiological salt [saline] solution or alcohols such as ethanol, propanol, and glycerol, in addition, sugar solutions such as glucose or mannitol solutions, or a mixture of the various aforementioned solvents, can be used.

The invention is explained in more detail below with the aid of examples.

Example 1

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxyethoxymethyl]-3-methylisoxazole

3.9 g (0.09 mol) sodium hydride (55-60%) are washed with petroleum ether and are added to 10 mL THF (pure); a solution of 18.6 g (0.09 mol) 2-[4-(4,5-dihydro-2-oxazolyl)phenoxy]ethanol in 100 mL THF (pure) is added in drops at approximately 20°C. The temperature thereby rises to 42°C. The mixture is stirred, under reflux, for 20 minutes; without heating, a solution of 15.8 g (0.09 mol) 5-bromomethyl-3-methylisoxazole, dissolved in 15 mL THF (pure), is then slowly added in drops. By the exothermic reaction, the temperature rises to 68°C. Subsequently, the reaction mixture is stirred, under reflux, for 1 hour and allowed to stand at room temperature overnight. The reaction material is then added to 500 mL ice water; the deposited precipitate is suctioned off, then washed with water. After drying at room temperature, the product from ethyl acetate is dissolved and recrystallized. Yield: 19 g, melting point: 98-101°C.

Example 2

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxypropionoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 1 from 3-[4-(4,5-dihydro-2-oxazolyl)phenoxy]propanol and 5-bromomethyl-3-methylisoxazole. Melting point : 70-74°C.

Example 3

5-[4-(4,5-dihydro-2-oxazolyl)phenoxybutoxymethyl]-3-methylisoxazole

0.96 g (0.022 mol) sodium hydride (55-60%) are suspended in 10 mL DMF (pure); 4.7 g (0.02 mol) 4-[4-(4,5-dihydro-2-oxazolyl)phenoxy]butanol, dissolved in 60 mL DMF (pure), are added in drops, at room temperature, while stirring. Stirring is carried out at 40°C for 20 minutes; then at 50-60°C, for 30 minutes. A solution of 3.52 g (0.02 mol) 5-bromomethyl-3-methylisoxazole in 10 mL DMF (pure) is added in drops to this mixture; subsequently, stirring is carried out at 70°C

for 3 hours. The reaction mixture is cooled, poured into 100 g ice water, and extracted with ether. The organic phase is dried over MgSO_4 and evaporated under vacuum. The oily residue (4.4 g) is purified chromatographically via a 120-g silica gel (Amicon-Grace, 70-200 μ) column (mobile solvent: methylene chloride/methanol mixture, 9:1). Yield: 2.0 g, melting point: 49-51°C.

Example 4

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxy]pentoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 3 from 5-[4-(4,5-dihydro-2-oxazolyl)phenoxy]pentanol and 5-bromomethyl-3-methylisoxazole. Melting point: 58-60°C.

Example 5

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxy]hexoxymethyl]-3-methylisoxazole

The title compound is analogous to Example 3 from 6-[4-(4,5-dihydro-2-oxazolyl)phenoxy]hexanol and 5-bromomethyl-3-methylisoxazole. Melting point: 68-72°C.

Example 6

5-[2-Chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]ethoxymethyl]-3-methylisoxazole

1.1 g (0.024 mol) sodium hydride (55-60%) are washed with petroleum ether and suspended in 10 mL THF (pure) under argon. A solution of 4.8 g (0.02 mol) 2-[2-chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]ethanol in 40 mL THF (pure) is added in drops, while stirring, then the reaction mixture is stirred, under reflux, for 30 minutes. A solution of 4.5 g (0.024 mol) 5-bromomethyl-3-methylisoxazole in 10 mL THF (pure) is then added in drops to this mixture and stirred, under reflux, for 4 hours. The reaction material is then evaporated under vacuum; the residue is stirred in ice water and the precipitate is suctioned off. The product thus obtained is purified via an 80-g silica gel (Amicon-Grace, 70-200 μ) column (mobile solvent: methylene chloride/ethyl acetate mixture, 1:1). The product is dissolved and recrystallized from methanol. Yield: 4.4 g. Melting point: 96-98°C.

Example 7

5-[2-Chloro-4-(4, 5-dihydro-2-oxazolyl)phenoxy]propoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 6 from 3-[2-chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]propanol and 5-bromomethyl-3-methylisoxazole. Melting point: 98-101°C.

Example 8

5-[2-Chloro-4-(4,5-dihydro-2-oxazolyl)phenoxybutoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 6 from 4-[2-chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]butanol and 5-bromomethyl-3-methylisoxazole. Melting point: 77-80°C.

Example 9

5-[2-Chloro-4-(4,5-dihydro-2-oxazolyl)phenoxypropoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 6 from 5-[2-chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentanol and 5-bromomethyl-3-methylisoxazole. Melting point: 89-91°C.

Example 10

5-[2-Chloro-4-(4,5-dihydro-2-oxazolyl)phenoxyhexyloxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 6 from 6-[2-chloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]hexanol and 5-bromomethyl-3-methylisoxazole. Melting point: 46-48°C.

Example 11

5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxypropoxymethyl]-3-methylisoxazole

2.9 g (0.01 mol) 3-(2,6-dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy)propanol and 3.62 g (0.02 mol) 5-bromomethyl-3-methylisoxazole are added in 40 mL pure THF; 0.52 g (0.012 mol) sodium hydride (55-60%) are introduced in portions, while stirring, at 15-20°C. Stirring is carried out at approximately 20°C for 24 hours, then this is carefully poured into 100 g ice water. The mixture is extracted with methylene chloride; the organic phase is washed with a saturated NaCl solution, then dried over MgSO₄ and evaporated under vacuum. The residue is chromatographed via a 200-g silica gel (Amicon-Grace, 70-200 μ) column (eluted first with methylene chloride and subsequently with a

methylene chloride/methanol mixture, 99:1). After evaporating the solvent under vacuum, the substance remains as a pure solid product. Yield: 1.05 g. Melting point: 60-64°C.

Example 12

5-[2,6-dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxybutoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 11 from 4-[2,5-dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]butanol and 5-bromomethyl-3-methylisoxazole. Melting point: 67-71°C.

Example 13

5-[2,5-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxyptyloxymethyl]-3-methylisoxazole

1.1 g (0.024 mol) sodium hydride (55-60%) are washed with pentane under an argon atmosphere and suspended in 10 mL pure dimethoxyethane. A solution of 6.4 g (0.02 mol) 5-[2,6-dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentanol in 30 mL dimethoxyethane is added in drops at approximately 25°C. The suspension is stirred at 50-60°C for 1 hour; a solution of 4.4 g (0.024 mol) 5-bromomethyl-3-methylisoxazole in 10 mL dimethoxyethane are added dropwise and stirring is carried out, under reflux, for 5 hours. Subsequently, the solvent is evaporated under vacuum; the solid residue is mixed with ice water and extracted with methylene chloride. After evaporating the solvent, the residue is stirred with ether; filtered off from the undissolved product; and the filtrate is again evaporated. The residue thus obtained is chromatographed via an 80-g silica gel (Amicon-Grace, 70-200 μ) column (mobile solvent: ethyl acetate-cyclohexane mixture, 6:4). Melting point: 39-41°C.

Example 14

5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxyhexyloxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 13 from 6-[2,6-dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]hexanol and 5-bromomethyl-3-methylisoxazole. The product is oily.

Example 15

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxyethoxymethyl]-3-(4-tolyl)isoxazole

0.44 g (0.01 mol) sodium hydride (55-60%) is washed with petroleum ether and suspended in

10 mL THF (pure). A solution of 2.07 g (0.01 mol) 2-[4-(4,5-dihydro-2-oxazolyl)phenoxy]ethanol in 40 mL THF (pure) is added in drops, while stirring, and the mixture is stirred at 60°C for 20 minutes. The reaction mixture is then cooled to 20°C, and a solution of 2.52 g (0.01 mol) 5-bromomethyl-3-(4-tolyl)isoxazole in 10 mL THF (pure) is added in drops. Boiling is carried out, under reflux, for another 3 hours. Subsequently, the solvent is evaporated under vacuum, then the residue is poured in ice water. The precipitated product is suctioned off, dissolved, and recrystallized from methanol. Yield: 2.4 g. Melting point: 118-121°C.

Example 16

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxypropoxymethyl]-3-(4-tolyl)isoxazole

The title compound is prepared analogous to Example 15 from 3-[4-(4,5-dihydro-2-oxazolyl)phenoxy]propanol and 5-bromomethyl-3-(4-tolyl)isoxazole. Melting point: 123-125°C.

Example 17

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxybutoxymethyl]-3-(4-tolyl)isoxazole

The title compound is prepared analogous to Example 15 from 4-[4-(4,5-dihydro-2-oxazolyl)phenoxy]butanol and 5-bromomethyl-3-(4-tolyl)isoxazole. Melting point: 83-85°C.

Example 18

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxypropyloxymethyl]-3-(4-tolyl)isoxazole

The title compound is prepared analogous to Example 15 from 5-[4-(4,5-dihydro-2-oxazolyl)phenoxy]pentanol and 5-bromomethyl-3-(4-tolyl)isoxazole. Melting point: 113-115°C.

Example 19

5-[4-(4,5-Dihydro-2-oxazolyl)phenoxyhexyloxymethyl]-3-(4-tolyl)isoxazole

The title compound is prepared analogous to Example 15 from 6-[4-(4,5-dihydro-2-oxazolyl)phenoxy]hexanol and 5-bromomethyl-3-(4-tolyl)isoxazole. Melting point: 88-92°C.

Example 20

3-(4-Chlorophenyl)-5-[4-(4,5-dihydro-2-oxazolyl) phenoxyethoxymethyl]isoxazole

The title compound is prepared analogous to Example 15 from 2-[4-(4,5-dihydro-2-oxazolyl)phenoxy]ethanol and 5-bromomethyl-3-(4-chlorophenyl)isoxazole. Melting point: 124-126°C.

Example 21

3-(4-Chlorophenyl)-5-[4-(4,5-dihydro-2-oxazolyl) phenoxypropoxymethyl]isoxazole

The title compound is prepared analogous to Example 15 from 3-[4-(4,5-dihydro-2-oxazolyl)phenoxy]propanol and 5-bromomethyl-3-(4-chlorophenyl)isoxazole. Melting point: 120-122°C.

Example 22

3-(4-Chlorophenyl)-5-[4-(4,5-dihydro-2-oxazolyl) phenoxybutoxymethyl]isoxazole

The title compound is prepared analogous to Example 15 from 4-[4-(4,5-dihydro-2-oxazolyl)phenoxy]butanol and 5-bromomethyl-3-(4-chlorophenyl)isoxazole. Melting point: 89-91°C.

Example 23

3-(4-Chlorophenyl)-5-[4-(4,5-dihydro-2-oxazolyl) phenoxyptyloxymethyl]isoxazole

The title compound is prepared analogous to Example 15 from 5-[4-(4,5-dihydro-2-oxazolyl)phenoxy]pentanol and 5-bromomethyl-3-(4-chlorophenyl)isoxazole. Melting point: 117-120°C.

Example 24

3-(4-Chlorophenyl)-5-[4-(4,5-dihydro-2-oxazolyl) phenoxyhexyloxymethyl]isoxazole

The title compound is prepared analogous to Example 15 from 6-[4-(4,5-dihydro-2-oxazolyl)phenoxy]hexanol and 5-bromomethyl-3-(4-chlorophenyl)isoxazole. Melting point: 106-108°C.

Example 25

5-[2-Chloro-4-(4,5-dihydro-4-ethyl-2-oxazolyl)phenoxyethoxymethyl]-3-methylisoxazole

3.8 g (0.0117 mol) 3-Chloro-4-(3-methylisoxazole-5-yl-methoxyethoxy)benzimidomethyl ester and 1.04 g (0.0117 mol) 2-aminobutanol are heated, with the exclusion of moisture, at 120°C (bath temperature) for 4 hours; the product formed (oil) is chromatographed via an 80-g silica gel (Amicon-Grace, 70-200 μ) column (eluted first with methylene chloride, then with a methylene chloride-methanol mixture, 99:1). After evaporating the solvent, 2.1 g of the desired product are obtained pure. The product is oily.

Example 26

5-[2-Chloro-4-(4,5-dihydro-4-ethyl-2-oxazolyl)phenoxypropoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 25 from 3-chloro-4-(3-methylisoxazol-5-yl-methoxypropoxy)benzimidomethyl ester and 2-aminobutanol. Melting point: 53-55°C.

Example 27

5-[2-Chloro-4-(4,5-dihydro-4-ethyl-2-oxazolyl)phenoxybutoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 25 from 3-chloro-4-(3-methylisoxazol-5-yl-methoxybutoxy)benzimidomethyl ester and 2-aminobutanol. The product is oily.

Example 28

5-[2-Chloro-4-(4,5-dihydro-4-ethyl-2-oxazolyl)phenoxypentoxymethyl]-3-methylisoxazole

The title compound is prepared analogous to Example 25 from 3-chloro-4-(3-methylisoxazol-5-yl-methoxypentyloxy)benzimidomethyl ester and 2-aminobutanol. The product is oily.

Pharmacological examples

Antiviral effectiveness

The antiviral effect of the compounds in accordance with the invention was tested in in vitro experiments. The compounds in accordance with the invention were poured, in various dilutions, into cell cultures of HeLa cells in microtiter plates. After 3 hours, the cultures were infected with

various human-pathogen rhinoviruses and other picornaviruses. 48-72 hours after the infection, the success of the therapy was determined, microscopically, by examining the cytopathogenic effect, and photometrically, according to neutral red [exposure] photographs (color test according to Finger) (Finter, N. B., in "Interferons" (N. B. Finter et al.), North Holland Publishing Co., Amsterdam (1966)).

The minimal concentration at which approximately half of the infected cells did not exhibit a cytopathogenic effect is considered as the minimal inhibition concentration (MIC). The results are compiled in Table I.

Table I

Substance from Example	MIC ($\mu\text{g/mL}$) HRV 2	HRV 3	HRV 11	Polio-V Type I	Coxsackie A 15	B4	DTM ($\mu\text{g/mL}$)
2	133.3	0.18	14.8	133.3	14.8	–	133.3
4	44.4	4.94	44.4	–	4.94	–	133.3
5	14.8	1.65	14.8	–	14.8	–	133.3
7	0.55	0.18	0.55	–	4.44	14.8	133.3
8	0.55	0.55	0.55	–	4.94	4.94	133.3
9	0.55	1.65	0.55	–	4.94	4.94	≥ 400.0
10	14.8	44.4	4.94	–	133.3	133.3	133.3
11	0.18	1.65	1.65	400.0	133.3	44.4	≥ 400.0
12	0.18	0.55	0.55	–	44.4	14.8	133.3
13	1.65	44.4	4.94	–	133.3	133.3	≥ 400.0
14	0.18	14.8	0.55	–	44.4	44.4	133.3
15	–	0.18	–	–	4.94	400.0	≥ 400.0
16	–	0.18	–	–	133.3	400.0	≥ 400.0
17	–	4.94	–	400.0	44.4	–	≥ 400.0
18	–	14.8	–	–	133.3	–	≥ 400.0
19	–	44.4	–	–	44.4	–	≥ 400.0
20	–	0.18	–	–	14.8	400.0	≥ 400.0
21	–	1.65	–	–	400.0	400.0	≥ 400.0
23	–	44.4	–	–	400.0	–	≥ 400.0
25	1.65	4.94	14.8	400.0	133.3	–	≥ 400.0
26	1.65	0.18	4.94	133.3	44.4	–	133.3
27	14.8	44.4	4.94	–	–	400.0	≥ 400.0

– = ineffective

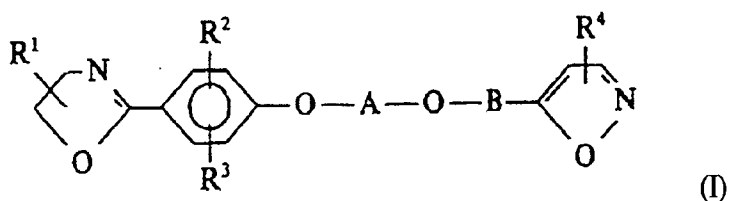
HRV = Human rhinovirus

MIC = Minimal inhibition concentration

DTM [MTD] = Maximum tolerance dose

Patent claims

1. Isoxazole derivatives of formula I:



in which

A denotes a branched or unbranched alkylene group with 2 to 12 C atoms;

B, a branched or unbranched alkylene group with 1 to 4 C atoms;

R¹, hydrogen, C₁-C₆-alkyl, or C₁-C₄-alkoxy;

R² and/or R³, hydrogen, F, Cl, Br, I, trifluoromethyl, C₁-C₆-alkyl, or C₁-C₄-alkoxy; and

R⁴, hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, or an aromatic hydrocarbon radical with up to 16 C atoms, which can also be substituted, up to three times, with F, Cl, Br, I, trifluoromethyl, C₁-C₄-alkyl, or C₁-C₄-alkoxy;

and their physiologically acceptable salts.

2. Isoxazole derivatives of formula I, according to Claim 1, characterized in that it has at least one of the following features:

A is a branched or unbranched alkylene chain with 2 to 6 C atoms;

B is a methylene or ethylene group;

R¹ is a C₁-C₃-alkyl group;

R² and/or R³ is hydrogen, Cl, or C₁-C₃-alkyl;

R⁴ is a C₁-C₃-alkyl group or a phenyl radical, which can be substituted with up to three C₁-C₃-alkyl groups containing chlorine atoms.

3. Isoxazole derivatives of formula I, according to Claim 1, characterized in that they have at least one of the following features:

A is an unbranched alkylene chain with 2 to 6 C atoms;

B is a methylene group;

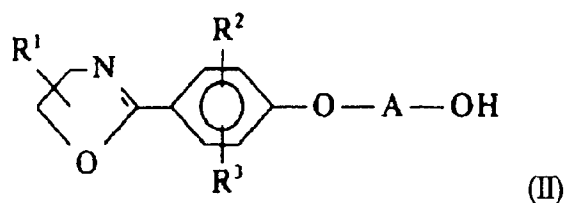
R is a C₁-C₃-alkyl group in the 4 position;

R² and/or R³ is hydrogen or Cl in the 2 or 6 position;

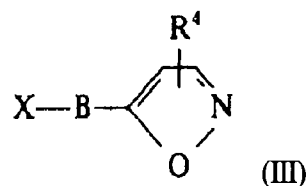
R⁴ is a C₁-C₃-alkyl group in the 3 position or a phenyl group, which can be substituted in the p position with a methyl group.

4. Method for the preparation of a compound of formula I, according to Claim 1,

characterized in that a compound of formula II:



in which the substituents have the meanings mentioned in Claim 1, is reacted with a compound of formula III:

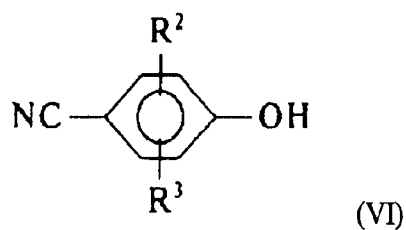


in which X is F, Cl, Br, or I, and R⁴ and B have the meanings mentioned in Claim 1.

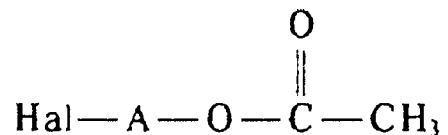
5. Method according to Claim 4, characterized in that the reaction is carried out in a solvent in the presence of a base.

6. Method for the preparation of compounds of formula I, according to Claim 1, characterized in that at least one of the following reactions is carried out:

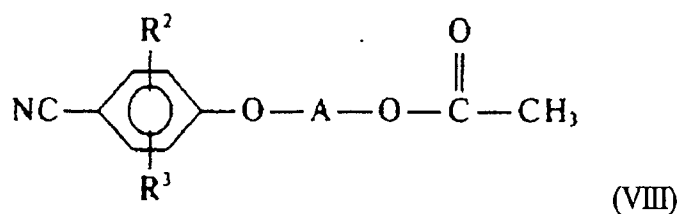
a) reaction of a compound of formula VI:



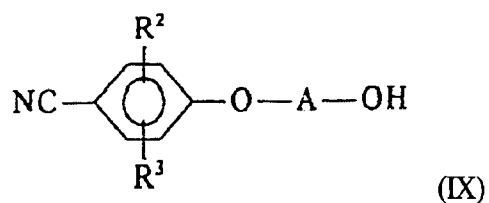
with a compound of formula VII:



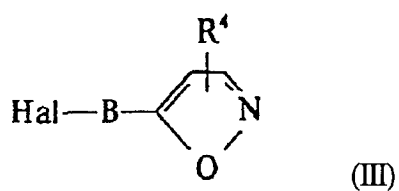
to form a compound of formula VIII:



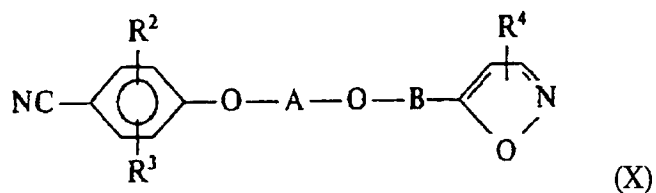
b) hydrolysis of the compound of formula VIII to form the compound of formula IX:



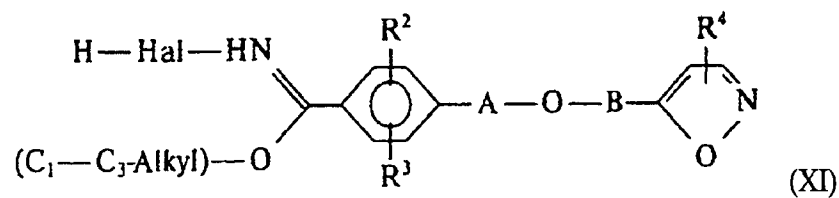
c) reaction of a compound of formula IX with a compound of formula III:



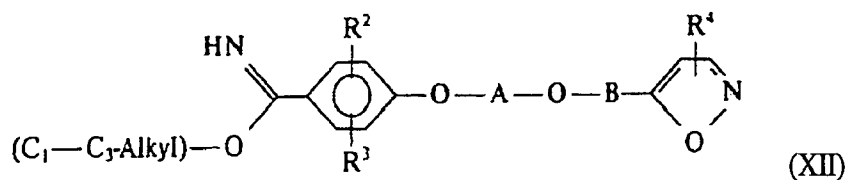
to form a compound of formula X:



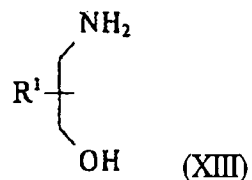
d) reaction of a compound of formula X with an alcohol to form a compound of formula XI:



e) reaction of a compound of formula XI to form a compound of formula XII:

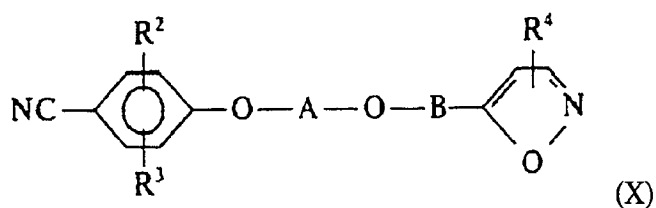


f) reaction of a compound of formula XII with a compound of formula XIII:



to form a compound of formula I according to Claim 1,
wherein the substituents R^1 to R^4 and A and B have the meanings mentioned in Claim 1 for formula I.

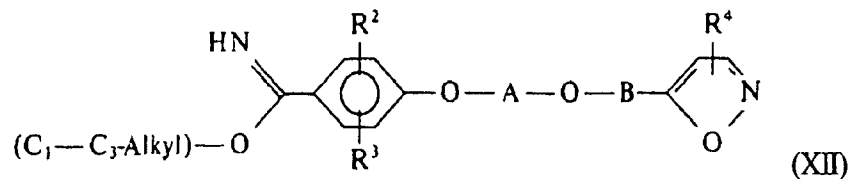
7. Compounds of formula X:



in which the substituents R^2 to R^4 , A, and B have the meanings mentioned in Claim 1.

8. Method for the preparation of compounds of formula X according to Claim 7,
characterized in that the reaction c) is used in accordance with Claim 6.

9. Compounds of formula XII:



in which the substituents R^2 to R^4 , A, and B have the meanings mentioned in Claim 1, and their acid addition salts.

10. Method for the preparation of compounds of formula XII, characterized in that the reactions d) and/or e) are/is used according to Claim 6.

11. Medicine, characterized in that it contains at least one compound of formula I according to Claim 1 and/or at least one of their physiologically acceptable salts, optionally in addition to other auxiliaries and/or carrier substances.

12. Medicine according to Claim 11, characterized in that it contains antivirally effective quantities of at least one compound according to Claim 1 and/or at least one of their physiologically acceptable salts.

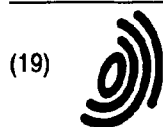
13. Use of compounds of formula I according to Claim 1 or their physiologically acceptable salts for the production of medicines.

14. Use of compounds of formula I according to Claim 1 for the treatment or prophylaxis of diseases caused by viral infection.

15. Use of compounds of formula I according to Claim 1 for the treatment or prophylaxis of diseases caused by infection with picornaviruses.

16. Use of compounds of formula I according to Claim 1 for the treatment or prophylaxis of diseases caused by infection with rhinoviruses.

17. Method for the production of medicines, characterized in that at least one compound of formula I or at least one of their physiologically acceptable salts is formed into a suitable administration form with physiologically acceptable auxiliaries and/or carrier substances.



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 123 933 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
16.08.2001 Bulletin 2001/33

(21) Application number: 01109746.6

(22) Date of filing: 06.10.1995

(51) Int Cl.7: **C07D 405/12**, C07D 311/64,
C07D 311/58, C07D 213/38,
C07D 333/20, C07C 211/27,
A61K 31/44, A61K 31/35

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE**
Designated Extension States:
LT LV SI

(30) Priority: 14.10.1994 EP 94116223

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
95115779.1 / 0 707 007

(71) Applicant: **MERCK PATENT GmbH**
64293 Darmstadt (DE)

(72) Inventors:
• **Böttcher, Henning, Dr.**
64287 Darmstadt (DE)

- **Devant, Ralf, Dr.**
64293 Darmstadt (DE)
- **Greiner, Hartmut, Dr.**
64331 Weiterstadt (DE)
- **Bartoszyk, Gerd**
64331 Weiterstadt (DE)
- **Berthelon, Jean-Jacques, Dr.**
69005 Lyon (FR)
- **Noblet, Marc**
69008 Lyon (FR)
- **Zeiller, Jean-Jacques**
69100 Villenbonne (FR)
- **Brunet, Michel**
69780 Toussieu (FR)

Remarks:

This application was filed on 20 - 04 - 2001 as a
divisional application to the application mentioned
under INID code 62.

(54) **2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chromane as CNS active agent**

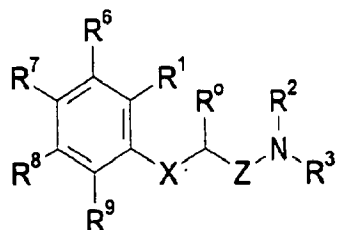
(57) 2-[5-(4-fluorophenyl)-3-pyridyl-methylami-
nomethyl]-chromane and its physiologically acceptable
salts thereof and (S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-

methylaminomethyl]-chromane and its physiologically
acceptable salts thereof are active on the central nerv-
ous system.

EP 1 123 933 A1

Description

[0001] The invention relates to novel amino(thio)ether derivatives of formula I



wherein

X is oxygen, sulphur, sulfinyl, sulfonyl or, in the case where R⁰ and R¹ are not together an alkylene chain with 1-3 atoms, also CH₂,

Z is -(CH₂)_{n1}-(CH₂)_{n2}-(CH₂)_{n3} with
 n₁ = 0, 1, 2 or 3;
 n₂ = 0 or 1;
 n₃ = 0, 1, 2 or 3 and the proviso that
 n₁ + n₂ + n₃ < 4,

R⁰ is hydrogen or A,

R¹ is hydrogen, A, OA, phenoxy, Ph, OH, F, Cl, Br, CN, CF₃, COOH, COOA, acyloxy with 1-4 C atoms, carboxamido, -CH₂NH₂, -CH₂NHA, -CH₂NA₂, -CH₂NHAc, -CH₂NHSO₂CH₃, or
 R⁰ and R¹ are together an alkylene chain with 1-3 C atoms or an alkenylene chain with 2-3 C atoms,

R² is hydrogen, A, Ac or -CH₂-R⁴,

R³ is -CH₂-R⁴, or -CHA-R⁴

R⁴ is Ph, 2-, 3- or 4-pyridyl which is unsubstituted or monosubstituted by R⁵, or thiophene which is unsubstituted, mono- or disubstituted by A, OA, OH, F, Cl, Br, CN and/or CF₃, or by another thienyl group,

R⁵ is a phenyl group which is unsubstituted, or mono-, di-, tri-, tetra- or pentasubstituted by F, CF₃, partially or completely fluorinated A, A and/or OA,

R⁶, R⁷, R⁸ and R⁹ are independently of each other H, A, OA, phenoxy, OH, F, Cl, Br, I, CN, CF₃, NO₂, NH₂, NHA, NA₂, Ac, Ph, cycloalkyl with 3-7 C atoms, -CH₂NH₂, -CH₂NHA, -CH₂NA₂, -CH₂NHAc or -CH₂NHSO₂CH₃ or two adjacent residues are together an alkylene chain with 3 or 4 C atoms, and/or

R¹ and R⁶ are together an alkylene chain with 3 or 4 C atoms,

A is alkyl with 1-6 C atoms,

Ac is alkanoyl having 1-10 C atoms or aroyl having 7-11 C atoms,

Ph is phenyl which is unsubstituted or substituted by R⁵, 2-, 3- or 4-pyridyl or phenoxy,

and the physiologically acceptable salts thereof.

[0002] The object of the invention was to find novel compounds capable of being used for the preparation of drugs.

[0003] It has been found that the compounds of formula I and their biocompatible acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphe (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (Apoplexia cerebri) such as stroke and cerebral ischaemia.

[0004] These substances can be used in the treatment of diseases which are related to interferences in the serotonergic and dopaminergic systems and which involve the receptors with high affinity to the 5-hydroxytryptamin (5HTIA

type) or/and dopamin (D2 type) receptors.

[0005] They are suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depression states, sexual dysfunctions caused by the central nervous system, disturbances in sleep or absorption of food. Furthermore, they are suitable to eliminate cognitive deficiencies, to improve powers of learning and memory and to treat Alzheimer's disease. They are also suitable for psychosis (schizophrenia).

[0006] Compounds of formula I and their biocompatible acid addition salts can therefore be used as active ingredients for anxiolytics, antidepressants, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

[0007] The invention relates to the amino(thio)ether derivatives of formula I and to their biocompatible acid addition salts.

[0008] The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. OA is preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA₂ is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

[0009] Ac is preferably alkonoyl having 1-6, in particular 1, 2, 3 or 4 C atoms, in detail preferably formyl or acetyl, furthermore, preferably propionyl, butyryl, isobutyryl, pentanoyl or hexanoyl, and in addition preferably benzoyl, o-, m- or p-toluylyl, 1- or 2-naphthoyl.

[0010] X is preferably oxygen or sulphur, whereas Z stands chiefly for -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CHCH₃)-, furthermore also preferably for -CH₂-(CHCH₃)-, -(CH₂)₂-(CHCH₃)-, -CH₂-(CHCH₃)-CH₂- or -(CHCH₃)-(CH₂)₂-.

[0011] The residue R⁰ is preferably H or methyl, but mostly R⁰ and R¹ are together an alkylene chain, preferably consisting of 2 C atoms. If R¹ is different from the meaning given previously it is preferably hydrogen, A, OA, CONH₂ or CN.

[0012] R² is preferably H or A and R³ is preferably 2-, 3- or 4-pyridylmethyl or phenyl which is substituted by another phenyl or furthermore, R³ is thienyl which is preferably substituted by another thienyl group.

[0013] The meaning of R³ is chiefly 2-, 3-, 4-pyridylmethyl, 5-phenyl-3-pyridylmethyl, 5-(fluorophenyl)-3-pyridylmethyl, 5-(methoxyphenyl)-3-pyridylmethyl, 4'-fluoro-3-biphenylmethyl, 3-biphenylmethyl or 4-(thienyl)-2-thienylmethyl. Furthermore, the meaning of R³ is preferably 2-, 4-, 5- or 6-(m-fluorophenyl)-3-pyridylmethyl, 3-, 4-, 5- or 6-(m-fluorophenyl)-2-pyridylmethyl or 2- or 3-(m-fluorophenyl)-4-pyridylmethyl whereby m stands for the prefixes mono-, di-, tri-, tetra- or penta-.

[0014] R⁶, R⁷, R⁸ and R⁹ are preferably independently of each other H, A, OA, Cl, CN or CF₃. Furthermore, R¹ and R⁶ are preferably together an alkylene chain with 4 C atoms. Furthermore, another preferred meaning is that two adjacent residues selected from R⁶, R⁷, R⁸ and R⁹ are together an alkylene chain with 3 or 4 C atoms.

[0015] Accordingly, the invention relates particularly to those compounds of formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to li, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, X is oxygen, R⁰ and R¹ are together -(CH₂)₂-, Z is methylene and R⁶, R⁷, R⁸ and R⁹ are hydrogen;

in Ib, X is oxygen, R⁰ and R¹ are together -(CH₂)₂-, Z is methylene and R⁴ is pyridyl or biphenyl which is unsubstituted or monosubstituted;

in Ic, X is oxygen, R⁰ and R¹ are together -(CH₂)₂-, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Id, X is oxygen, R⁰ and R¹ are together methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Ie, X is oxygen, R⁰ is hydrogen, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in If, X is oxygen, R⁰ and R¹ are hydrogen, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Ig, X is oxygen, R⁰ is hydrogen, R¹ is chlorine, ethyl or methoxy, Z is methylene and R⁴ is 4-(4-fluorophenyl)-3-pyridyl;

in Ih, X is oxygen, Z is methylene and R⁴ is 5-phenyl-3-pyridyl;

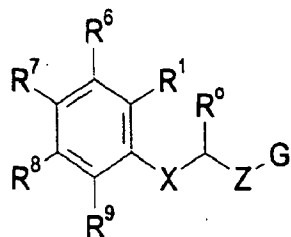
in Ii, X is oxygen, Z is -(CH₂)₂-, -(CH₂)₃- or -(CHCH₃)-, and R⁴ is 5-(4-fluorophenyl)-3-pyridyl,

and the salts thereof.

[0016] Especially preferred compounds are those of partial formulae Ik and lak to lik, which correspond to partial formulae I and Ia to li, but in which additionally:

5 X is sulphur, sulfinyl or sulfonyl.

[0017] The invention further relates to a process for the preparation of derivatives of formula I and their salts, characterized in that a compound of formula II



II,

wherein

G is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, especially a suitable leaving group, and R^0 , R^1 , R^6 , R^7 , R^8 , R^9 , X and Z are as defined,

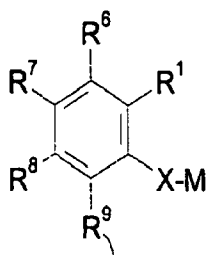
is reacted with an amine of formula III



III,

wherein

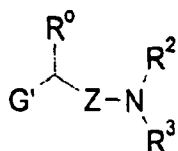
R^2 and R^3 are as defined, or in that a compound of the formula IV



IV,

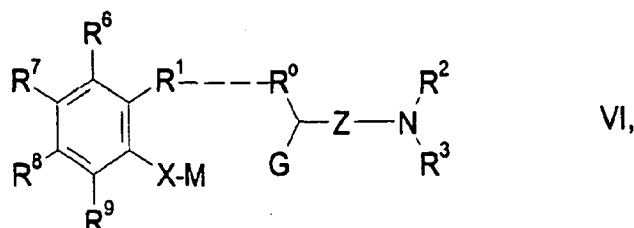
wherein,

M is H, Li^+ , Na^+ , K^+ , NH_4^+ or another suitable metal ion, and X, R^1 , R^6 , R^7 , R^8 and R^9 are as defined, is reacted with a compound of formula V



V,

wherein
 G' has the definitions given for G and R⁰, R², R³ and Z are as defined,
 or in that a compound of formula VI



wherein
 R⁰ and R¹ are together an alkylene chain with 1-3 C atoms, and R², R³, R⁶, R⁷, R⁸, R⁹, X, Z, M and G are as already defined,

is cyclised to an aminoether or aminothioether derivative of formula I, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds is treated with a reducing agent, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolizable groups is treated with a solvolizing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ar group is converted into another Ar group, and/or in that a resulting base or acid of formula I is converted into one of its salts by treatment with an acid or base.

[0018] The compounds of formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

[0019] If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of formula I.

[0020] In the derivatives of formula II, G is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulphonyloxy having 1-6 C atoms (e.g. methanesulphonyloxy) or arylsulphonyloxy having 6-10 C atoms (e.g. benzenesulphonyloxy, p-toluenesulphonyloxy, naphthalene-1- or -2-sulphonyloxy).

[0021] Some of the compounds of formulae II and, in particular, III are known; the unknown compounds of formulae II and III can easily be prepared analogously to the known compounds.

[0022] Primary alcohols of the formula II can be obtained e.g. by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds yields the corresponding halides of the compounds of the formula II. The corresponding sulphonyloxy compounds can be obtained from the alcohols of formula II by reaction with the appropriate sulphonyl chlorides.

[0023] The iodine compounds of the formula 7 can be obtained e.g. by reacting potassium iodide with the appropriate p-toluenesulphonic acid esters.

[0024] Most of the amine derivatives III are known and can be obtained e.g. by alkylation or acylation of known amines.

[0025] The reaction of the compounds II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component. The reaction time is between a few minutes and 14 days, depending on the conditions used, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

[0026] It is also possible to obtain a compound of formula I by reacting a compound of formula IV with a compound of formula G'(CHR^o)-Z-NR²R³ (V).

[0027] Some of the compounds of formulae V and, in particular, IV are known; the unknown compounds can easily be prepared analogously to the known compounds. Thus, compounds of formula IV can easily be prepared by meta-

[0028] The amines of formula V can be prepared starting from a primary amine by means of the diverse possibilities of alkylation or acylation of amines known per se. It is also possible to convert appropriately substituted nitro compounds into the amines of formula V by reduction and subsequent alkylation.

[0029] The reaction of compounds IV and V proceeds according to methods which are known from the literature for the formation of ethers, thioethers or esters. The components can be melted with one another directly, without the presence of a solvent, if appropriate in a closed tube or in an autoclave, at normal pressure or at elevated pressure, an inert gas such as e.g. N₂ being added to increase the pressure. However, it is also possible to react the compounds in the presence of an inert solvent. Suitable solvents are those mentioned previously for the reaction of II with III. The addition of an acid-binding agent to the reaction mixture can also have a favourable effect. The same bases are suitable as those previously described for the reaction of compounds II and II.

[0030] Depending on the reaction conditions chosen, the optimum reaction time is between a few minutes and 14 days, and the reaction temperature is between about 0° and 150°, usually between 20° and 130°.

[0031] Furthermore, a compound of formula I can be obtained by cyclisation of a compound of formula VI wherein R^o and R¹ are together an alkylene chain with 1 to 3 C atoms.

[0032] Compounds of the formula VI can be obtained for example by the reduction of ketones which are similar to compound VI but wherein the CHG-group is replaced by a carbonyl group.

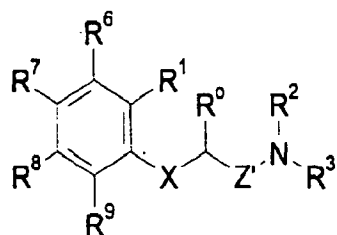
[0033] The cyclisation reaction of a compound of the formula VI proceeds according to the methods described previously for the reaction of the compounds IV and V under equal reaction conditions.

[0034] A compound of formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds, with a reducing agent, preferably at temperatures of between -80 and +250°, in the presence of at least one inert solvent.

[0035] Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulphonyloxy (e.g. p-toluenesulphonyloxy), N-benzenesulphonyl, N-benzyl or O-benzyl.

[0036] In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of formula I by reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is for example carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

[0037] Preferred starting materials for the reduction have formula VII



VII

wherein

Z' is a chain which corresponds to the radical Z except that one or more -CH₂ groups have been replaced by -CO- and/or one or more hydrogen atoms have been replaced by Cl, Br, F, SH, or OH groups.

Compounds of formula VII can be obtained by amidation of acids, acid halides, anhydrides or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an

amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of between about -10 and 40, preferably of between 0 and 30°.

[0038] If nascent hydrogen is used as the reducing agent, this can be produced e.g. by treating metals with weak acids or with bases. Thus it is possible e.g. to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminium-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminium amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

[0039] Other reducing agents which can be used to particular advantage are complex metal hydrides such as LiAlH_4 , NaBH_4 , diisobutylaluminium hydride or $\text{NaAl}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2\text{H}_2$, and diborane, catalysts such as BF_3 , AlCl_3 or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with NaBH_4 are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of between -80 and +150°, especially of between about 0 and about 100°.

[0040] The reduction of -CO groups in acid amides (e.g. those of formula VI in which Z' is a $-(\text{CH}_2)_{n1}(\text{CHA})_{n2}-\text{CO}$ group) to CH_2 groups can be carried out to particular advantage with LiAlH_4 in THF at temperatures of between about 0 and 66°.

[0041] It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner method, e.g. by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of between about 150 and 250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3-4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulphoxide at room temperature.

[0042] Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as e.g. Raney Ni or Pd. In this way, e.g. Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

[0043] Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of formula I.

[0044] The starting materials for the solvolysis can be obtained for example by reacting III with compounds which have formula II except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylamine derivatives (which have formula I except that, in the 1-position of the radical, they contain an acyl group, preferably an alkanoyl, alkylsulphonyl or arylsulphonyl group having up to 10 C atoms in each case, such as methanesulphonyl, benzenesulphonyl or p-toluene-sulphonyl) can be hydrolyzed to give the corresponding secondary amine derivatives e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of between 0 and 200°. Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulphones such as tetramethylene sulphone; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

[0045] A compound of formula I can furthermore be converted to another compound of formula I by methods known per se.

[0046] Compounds of formula I in which for example R^2 is hydrogen can be converted to compounds with tertiary amino groups by alkylation or acylation of the secondary amino residue in an inert solvent, e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of between about -10 and the boiling point of the solvent, preferably of between 0 and 70°. Furthermore, other primary amino groups can be transformed to secondary or tertiary amino groups by the known alkylation reactions.

[0047] Compounds of formula I can also be converted into other derivatives of formula I by transformations at the radical Ar.

[0048] Ethers of formula I in which the radical Ph is mono- or disubstituted by O-alkyl can be cleaved, the corresponding hydroxy derivatives being formed. It is possible, e.g. to cleave the ethers by treatment with dimethyl sulphideboron tribromide complex, for example in toluene, ethers such as THF or dimethyl sulphoxide, or by melting with pyridine or aniline hydrohalides, preferably pyridine hydrochloride, at about 150-250°.

[0049] If other side reactions in the compounds of formula I are to be excluded, the radicals Ph can be chlorinated, brominated or alkylated under the conditions of the Friedel-Crafts-reactions, by reacting the appropriate halogen or

alkyl chloride or alkyl bromide under the catalysis of Lewis acids, such as e.g. AlCl_3 , FeBr_3 or Fe, at temperatures between 30° and 150° , expediently between 50° and 150° in an inert solvent, such as e.g. hydrocarbons, THF or carbon tetrachloride, with the compound of the formula I to be derivatised. Moreover, it is for example possible to reduce a nitro group to an amino group by the reactions known per se.

[0050] The compounds of formula I can possess one or more centres of asymmetry. When prepared, they can therefore be obtained as racemates or else in the optically active form if optically active starting materials are used. When synthesized, compounds possessing two or more centres of asymmetry are generally obtained as mixtures of racemates, from which the individual racemates can be isolated in the pure form, for example by recrystallization from inert solvents. If desired, the racemates obtained can be chemically or by crystallization of conglomerates resolved into their optical antipodes by the methods known per se. Preferably, diastereoisomers are formed from the racemate by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids such as the D and L forms of protected amino acid derivatives such as tosylproline, tartaric acid, dibenzoyltartaric acid, diacetyltartaric acid, camphor-sulphonic acids, mandelic acid, malic acid or lactic acid. The different forms of the diastereoisomers can be resolved in a manner known per se, e.g. by fractional crystallization, and the optically active compounds of formula I can be liberated from the diastereoisomers in a manner known per se.

[0051] A base of formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e. g. sulphuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i. e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulphonc or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemonosulphonic and naphthalenedisulphonic acids and laurylsulphuric acid.

[0052] If desired, the free bases of formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

[0053] The invention further relates to the use of the compounds of formula I and their biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate; in combination with one or more additional active ingredients.

[0054] The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of formula I and/or one of their biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

[0055] The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

[0056] The compounds of formula I and their biocompatible salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with α -methyl dopa). The compounds can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (Apoplexia cerebri), such as stroke and cerebral ischaemia.

[0057] Furthermore, they are suitable to eliminate cognitive deficiencies, to improve the power of learning and memory and to treat Alzheimer disease.

[0058] In these treatments, the substances of formula I of the invention are normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocomin), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

[0059] In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C.

Example 1

[0060] A solution of 2.8 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 2.2 g 3-(chloromethyl)-pyridine in 250 ml of DMF are stirred together with 1 g N-methyl-morpholine for 12 hours at 20° and worked up in a conventional manner to give N-(3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 163-164°.

[0061] The following are obtained analogously:

from 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-methoxyphenyl)-pyridine
N-[5-(4-methoxyphenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine, maleate, m.p. 177-178°;

from 2-aminomethyl-chromane and 3-(chloromethyl)-5-phenyl-pyridine
N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine, maleate, m.p. 184°;

from 2-aminoethyl-chromane and 3-(chloromethyl)-biphenyl N-3-biphenylethyl-N-(2-chromanyl-methyl)-amine, maleate, m.p. 162°;

from 2-aminomethyl-6-phenyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(6-phenyl-2-chromanyl-methyl)-amine, maleate, m.p. 222-224°;

from 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine, maleate, m.p. 182-183°;

from 2-aminomethyl-chromane and 3-(chloromethyl)-biphenyl
N-3-biphenylmethyl-N-(2-chromanyl-methyl)-amine, maleate, m.p. 174-175°;

from 2-aminomethyl-chromane and 3-(chloromethyl)-4'-fluorobiphenyl
N-(4'-fluoro-3-biphenylmethyl)-N-(2-chromanyl-methyl)-amine, maleate, m.p. 183-184°

from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 160-165°;

from 2-aminomethyl-7-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(7-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 170,5-172°;

from 2-aminomethyl-6-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-methoxy-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-5-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(5-methoxy-chroman-2-yl)-methyl]-amine, maleate, m.p. 181-183°;

from 2-aminomethyl-8-nitro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-nitro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-2,3,4,5-tetrahydro-1-benzoxepine and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[2-(2,3,4,5-tetrahydro-1-benzoxepinyl)-methyl]-amine, maleate, m.p. 194-195°;

5 from 2-aminoethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanylethyl)-amine, maleate, m.p. 160°;

from 3-amino-2,3,4,5-tetrahydro-1-benzoxepine and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-3-(2,3,4,5-tetrahydro-1-benzoxepinyl)-amine, maleate, m.p. 179-180°;

10 from 2-aminomethyl-8-hydroxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-hydroxy-2-chromanyl)-methyl]-amine, maleate, m.p. 173°;

15 from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-fluorobiphenyl
N-(4'-fluoro-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 176°;

from 2-aminomethyl-6-fluorochromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-fluoro-2-chromanyl)-methyl]-amine, maleate, m.p. 169-170°;

20 from 2-aminomethyl-chromane and 3-(2-pyridyl)-chloromethyl-benzene
N-[3-(2-pyridyl)-phenylmethyl]-N-2-chromanyl-methyl-amine, maleate, m.p. 201°;

from 2-aminomethyl-chromane and 3-(3-pyridyl)-chloromethyl-benzene
N-[3-(3-pyridyl)-phenylmethyl]-N-2-chromanyl-methyl-amine, dimaleate, m.p. 120°;

25 from 2-aminomethyl-8-methoxy-chromane and 3-(3-pyridyl)-chloromethyl-benzene
N-[3-(3-pyridyl)-phenylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 85°;

30 from 2-aminomethyl-8-methoxy-chromane and 3-(2-pyridyl)-chloromethyl-benzene
N-[3-(2-pyridyl)-phenylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 167°.

[0062] The following are obtained analogously (instead of maleic acid the compounds were treated with 0,1 n HCl solution to give the hydrochlorides):

35 from 2-aminomethyl-chromane and 3-(chloromethyl)-4'-methyl-biphenyl N-(4'-methyl-3-biphenylmethyl)-N-2-chromanyl-methyl-amine, hydrochloride, m.p. 206-207°;

from 2-aminomethyl-chromane and 3-(chloromethyl)-4'-methoxy-biphenyl N-(4'-methoxy-3-biphenylmethyl)-N-2-chromanyl-methyl-amine, hydrochloride, m.p. 191-192°;

40 from 2-aminomethyl-chromane and 3-(chloromethyl)-4'-trifluoromethyl-biphenyl
N-(4'-trifluoromethyl-3-biphenylmethyl)-N-2-chromanyl-methyl-amine, hydrochloride, m.p. 181-182°;

45 from 2-aminomethyl-chromane and 3-(chloromethyl)-3'-trifluoromethyl-biphenyl
N-(3'-trifluoromethyl-3-biphenylmethyl)-N-2-chromanyl-methyl-amine, hydrochloride, m.p. 161-162°;

from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-trifluoromethyl-biphenyl
N-(4'-trifluoromethyl-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, hydrochloride, m.p. 206-207°;

50 from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-3'-trifluoromethyl-biphenyl
N-(3'-trifluoromethyl-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, hydrochloride, m.p. 206°;

55 from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-methylbiphenyl
N-(4'-methyl-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, hydrochloride, m.p. 188-189°;

from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-methoxy-biphenyl
N-(4'-methoxy-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, hydrochloride, m.p. 186-187°;

from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-biphenyl
N-(3-biphenylmethyl)-N-[(8-methoxy-2-chroman-yl)-methyl]-amine, hydrochloride, m.p. 211-212°.

from 2-aminomethyl-6-nitro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-nitro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-7-nitro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(7-nitro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-8-chloro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-chloro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-6-chloro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-chloro-chroman-2-yl)-methyl]-amine, m.p. 78-80°;

from 2-aminomethyl-7-chloro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(7-chloro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-8-cyano-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-cyano-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-6-cyano-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-cyano-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-5-cyano-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(5-cyano-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-5-fluoro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(5-fluoro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-6-fluoro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-fluoro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-chromane and 3-(chloromethyl)-5-(3,4-difluorophenyl)-pyridine
N-[5-(3,4-difluorophenyl)-3-pyridylmethyl]-N-(2-chromane-methyl)-amine, maleate, m.p. 175-177°;

from 2-aminomethyl-chromane and 3-phenoxy-benzylchloride
N-(3-phenoxy-benzyl)-N-(2-chromane-methyl)-amine, maleate, m.p. 150-152°;

from 2-aminomethyl-chromane and 2-(chloromethyl)-4-phenyl-pyridine
N-(4-phenyl-2-pyridylmethyl)-N-(2-chromane-methyl)-amine, maleate, m.p. 156-158°;

from 2-aminomethyl-6-bromo-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[2-(6-bromo-chromane)-methyl]-amine, maleate;

from 2-aminomethyl-benzofurane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-benzofurane-methyl)-amine, maleate, m.p. 147°;

from 2-aminomethyl-7-fluoro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(7-fluoro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-8-fluoro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-fluoro-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-6-trifluoromethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-trifluoromethyl-chroman-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-8-trifluoromethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine

N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-trifluoromethyl-chroman-2-yl)-methyl]-amine, maleate.

Example 2

5 [0063] By reaction of 2-aminomethyl-2,3-dihydrobenzofuran with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1, N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydrobenzofuran-2-yl)-methyl]-amine is obtained, maleate, m.p. 178-180°.

[0064] The following are obtained analogously:

10 from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(4-methoxyphenyl)-pyridine
N-[5-(4-methoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(3,4-dimethoxyphenyl)-pyridine
N-[5-(3,4-dimethoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzo-furan-2-yl)-methyl]-amine, maleate;

15 from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(2,4-dimethoxyphenyl)-pyridine
N-[5-(2,4-dimethoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzo-furan-2-yl)-methyl]-amine, maleate;

20 from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(3,4,5-trifluorophenyl)-pyridine
N-[5-(3,4,5-trifluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzo-furan-2-yl)-methyl]-amine, maleate;

from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(2,3,4,5,6-pentafluorophenyl)-pyridine
N-[5-(2,3,4,5,6-pentafluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate.

25 Example 3

[0065] A mixture of 2,2 g 3-methyl-phenol, preferably the sodium salt thereof, and 5,6 g N-(2-chloroethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine ("A") [obtainable by reaction from phthalimid potassium salt and 5-(4-fluorophenyl)-3-chloromethyl-pyridine, cleavage of the product with hydrazine and subsequent reaction with 1,2-dichloroethane] in 50 ml acetonitrile is stirred for 5 hours at 50° and worked up in the conventional manner.

30 [0066] N-[2-(3-methylphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine is obtained. Stirring with 0,5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 152-154°.

[0067] The following are obtained analogously:

35 from 2,4-dichlorophenol sodium salt and "A"
N-[2-(2,4-dichlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, maleate, m.p. 148-150°;

from 3-methoxyphenol sodium salt and "A"
N-[2-(3-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, maleate, m.p. 122-124°;

40 from 4-methoxyphenol sodium salt and "A"
N-[2-(4-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, m.p. 94-96°;

45 from 3-chlorophenol sodium salt and "A"
N-[2-(3-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 150-152°;

from 2-chlorophenol sodium salt and "A"
N-[2-(2-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 153-155°;

50 from 2-methoxyphenol sodium salt and "A"
N-[2-(2-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, maleate, m.p. 134-136°;

from 4-chlorophenol sodium salt and "A"
N-[2-(4-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 163-164°;

55 from 2-ethylphenol sodium salt and "A"
N-[2-(2-ethylphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 128-130°;

from 3-cyanophenol sodium salt and "A"

N-[2-(3-cyanophenol)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 245°;

from 4-cyanophenol sodium salt and "A"

5 N-[2-(4-cyanophenol)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 250°;

from phenol sodium salt and N-[3-phenoxy-benzyl]-amine N-(2-phenoxy-ethyl)-N-(3-phenoxy-benzyl)-amine, maleate, m.p. 166-168°;

10 from phenol sodium salt and "A"

N-(2-phenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 84-86°.

Example 4

15 **[0068]** By reaction of 2-aminomethyl-6-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-methoxy-2-chromanyl)-methyl]-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride, m.p. 205-206°.

Example 5

20 **[0069]** By reaction of 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride-hemihydrate, m.p. 210-213°.

Example 6

[0070] A solution of 1,8 g 3-aminomethyl-biphenyl [obtainable by reducing 3-cyano-biphenyl] and 1,6 g 2-chloroethyl-phenylether [obtainable by reaction of sodium-phenolate with dichloroethane] in 200 ml of acetonitrile is stirred for 8 hours at room temperature and worked up in a conventional manner to give N-(3-biphenylmethyl)-N-2-phenoxyethyl-amine. Stirring with 0,5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 178-180°.

30 **[0071]** The following are obtained analogously:

from 3-aminomethyl-4'-fluoro-biphenyl and 2-chloroethyl-phenylether
N-(4'-fluoro-3-biphenylmethyl)-N-2-phenoxyethyl-amine, maleate, m.p. 194-196°;

35

from 3-aminomethyl-2',4'-difluoro-biphenyl and 2-chloroethyl-phenylether
N-(2',4'-difluoro-3-biphenylmethyl)-N-2-phenoxyethyl-amine;

from 3-aminomethyl-5-phenylpyridine and 2-chloroethyl-phenylether
N-(5-phenyl-3-pyridylmethyl)-N-2-phenoxyethyl-amine, m.p. 77-79°;

40

from 2-aminomethyl-4-(3-thienyl)-thiophen and 2-chloroethyl-phenylether
N-[4-(3-thienyl)-2-thienylmethyl]-N-2-phenoxyethyl-amine, m.p. 96-98°;

45

from 2-aminomethyl-4-methyl-thiophen and 2-chloroethyl-phenylether
N-(4-methyl-2-thienylmethyl)-N-2-phenoxyethyl-amine;

from 2-aminomethyl-4-methoxy-thiophen and 2-chloroethyl-phenylether
N-(4-methoxy-2-thienylmethyl)-N-2-phenoxyethyl-amine;

50

from 2-aminomethyl-4-ethyl-thiophen and 2-chloroethyl-phenylether
N-(4-ethyl-2-thienylmethyl)-N-2-phenoxyethyl-amine;

from 2-aminomethyl-4-chloro-thiophen and 2-chloroethyl-phenylether
N-(4-chloro-2-thienylmethyl)-N-2-phenoxyethyl-amine;

55

from 3-aminomethyl-4'-fluoro-biphenyl and 2-chloroethyl-(3-cyano-phenyl)-ether
N-(4'-fluoro-3-biphenylmethyl)-N-2-(3-cyano-phenoxy-ethyl)-amine, maleate, m.p. 158-160°;

from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-methoxy-phenyl)-ether
N-(3-biphenylmethyl)-N-2-(2-methoxy-phenoxy)-ethyl-amine, m.p. 72-74°;

5 from 3-aminomethyl-biphenyl and 2-chloroethyl-2-biphenyl-ether
N-(3-biphenylmethyl)-N-2-(2-biphenyloxy)-ethylamine, maleate, m.p. 146-148°;

from 3-aminomethyl-5-(4-fluoro-phenyl)-pyridine and 2-chloroethyl-(2-biphenyl)-ether
N-[5-(4-fluorophenyl-3-pyridylmethyl)]-N-2-(2-biphenyloxy)-ethylamine, m.p. 134-136°;

10 from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-hydroxyphenyl)-ether
N-(3-biphenylmethyl)-N-2-(2-hydroxyphenoxy)-ethylamine, m.p. 88-90°;

Example 7

15 **[0072]** A solution of 1,2 g 2-hydroxy-benzonitril and 2,5 g N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine [obtainable by reaction of 2-hydroxyethylamine with 3-chloromethyl-5-phenyl-pyridine and subsequent transformation of the product to the 2-chloroethyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine. Stirring with 0,5 equivalents of oxalic acid in 100 ml ethanol gives the oxalate, m.p. 208°.

20 **[0073]** The following are obtained analogously:

from 2-chloro-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-chlorophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

25 from 2-methyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-methylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-chloro-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-chlorophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

30 from 4-cyano-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

35 from 3-ethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(3-ethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-trifluoromethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-trifluoromethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

40 from 2-bromo-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-bromophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-aminomethyl-phenyl and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-aminomethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

45 from 4-methoxy-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-methoxyphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

50 from 3-aminomethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(3-aminomethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-aminomethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-aminomethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

55 Example 8

[0074] A mixture of 3,1 g N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine, 3 g NaOH, 50 ml of water and 40 ml of diethylene glycol monoethyl ether is stirred for 3 hours at a bath temperature of 140°. It is cooled

and worked up after a conventional manner, and N-[2-(2-carboxamidophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine is obtained. Stirring with 0,5 equivalents of oxalic acid in 100 ml ethanol gives the oxalate, m.p. 230°.

Example 9

[0075] Analogously to Example 8 N-[2-(4-carboxamidophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine is obtained by partial hydrolysis of N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 10

[0076] Starting from N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine analogously to Example 8, boiling for 16 hours and then working up in a conventional manner gives N-[2-(4-carboxyphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 11

[0077] Starting from N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine analogously to Example 8, boiling for 16 hours and then working up in a conventional manner gives N-[2-(2-carboxyphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 12

[0078] Analogously to Example 7 a solution of 2,3 g sodium phenolate and 2,5 g N-3-chloropropyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable by reaction of 3-hydroxypropylamine with 3-chloromethyl-5-(4-fluorophenyl)-pyridine and subsequent transformation of the product to the 3-chloropropyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-(3-phenoxy-propyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine. Stirring with 0,5 equivalents of oxalic acid in 100 ml ethanol/water mixture gives the oxalate-hemihydrate, m.p. 217°.

[0079] The following are obtained analogously:

from sodium phenolate and N-4-chlorobutyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]amine
N-(4-phenoxy-butyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 143°;

from sodium phenolate and N-2-chloroisopropyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine
N-(2-phenoxy-isopropyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 123-125°;

from sodium thiophenolate and N-2-chloroethyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine
N-(2-thiophenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 230°;

from sodium thiophenolate and N-4-chlorobutyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine;

from sodium thiophenolate and N-3-chloropropyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-(3-thiophenoxy-propyl)-N-(5-phenyl-3-pyridylmethyl)-amine;

from sodium thiophenolate and N-2-chloroisopropyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-(2-thiophenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)amine.

Example 13

[0080] According to Example 7 the following are obtained analogously:

from 2-chloro-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-chlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-methyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-methylchlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-chloro-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-chlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-cyano-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-cyanothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 3-ethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(3-ethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-trifluoromethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-trifluoromethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridyl-methyl)-amine;

from 2-bromo-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-bromothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(2-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-methoxy-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-methoxythiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 3-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(3-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine
N-[2-(4-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 14

[0081] A solution of 2,8 g N-[2-(2-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable according to Example 3] and one equivalent 3-chloromethyl-5-(4-fluorophenyl)-pyridine in 125 ml of acetonitrile are stirred for 6 hours at 40° and worked up in a conventional manner to give N-[2-(2-methoxyphenoxy)-ethyl]-N,N-bis-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 90-92°.

[0082] The following are obtained analogously by reaction with 3-chloromethyl-5-(4-fluorophenyl)-pyridine:

and N-(4-phenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine
N-(4-phenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(2-phenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)-amine
N-(2-phenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(2-thiophenoxy-ethyl)-N-(5-phenyl-3-pyridylmethyl)-amine
N-(2-thiophenoxy-ethyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine
N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

Example 15

[0083] Analogously to Example 7 a solution of 2,3 g sodium 1-naphtholate and 2,9 g N-2-chloroethyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable by reaction of 2-hydroxyethylamine with 3-chloromethyl-5-(4-fluorophenyl)-pyridine and subsequent transformation of the product to the 2-chloroethyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-[2-(1-naphthoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 92-94°.

[0084] The following are obtained analogously by reaction of 2-naphtholate

with N-2-chloroethyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine:
N[2-(2-naphthoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, m.p. 128-130°;

with N-2-chloroethyl-N-[5-(2,4-difluorophenyl)-3-pyridylmethyl]-amine:
N-[2-(2-naphthoxy)-ethyl]-N-[5-(2,4-difluorophenyl)-3-pyridylmethyl]-amine.

Example 16

[0085] A solution of 2.1 g N-(2-phenoxy-ethyl)-N-[5-(4-fluoro-phenyl)-3-pyridylmethyl]-amine [obtainable according to Example 3] in 100 ml THF is treated with 2 ml methyl iodide under stirring over a period of 3 hours. Working up in a conventional manner gives N-(2-phenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-methyl-amine, oxalate, m.p. 159-161°;

[0086] The following are obtained analogously by alkylation of the secondary amines:

N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-N-methylamine, m.p. 71°;

N-3-biphenylmethyl-N-(2-chromanyl-methyl)-N-methyl-amine.

Example 17

[0087] By reaction of N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine with 1-chloro-3-phenylpropane analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(3-phenylpropyl)-amine is obtained, m.p. < 50°.

Example 18

[0088] Analogously to Example 3 one obtains by reaction of

phenol sodium salt with N-(2-chloroethyl)-N-3-(2-pyridyl)-chloromethylbenzene
N-[3-(2-pyridyl)-phenylmethyl]-N-[2-(phenoxy)-ethyl]-amine, maleate, m.p. 170°;

phenol sodium salt with N-(2-chloroethyl)-N-3-(3-pyridyl)-chloromethylbenzene
N-[3-(3-pyridyl)-phenylmethyl]-N-[2-(phenoxy)-ethyl]-amine, maleate, m.p. 123-125°.

[0089] Preparation of enantiomeric compounds:

Example 19

[0090] A solution of 4.5 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 3.9 g tosylproline in 190 ml ethanol are refluxed for 15 minutes. Afterwards the solution is cooled down to 5° while it is stirred. During the cooling procedure a few crystall of pure (R)-2-aminomethyl-chromane were added. The solution was kept under stirring at 5° for a period of 18 hours and afterwards the pure enantiomer (R)-2-aminomethyl-chromane was separated. The crystallisation process was repeated two times with the crystall derived from the first crystallisation in order to yield an enantiomeric excess of more than 99 %.

[0091] Subsequently the (R)-2-aminomethyl-chromane was reacted with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 to give (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane [= (R)-(-)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine]. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 234-235°; $[\alpha]^{20}_D = -65^\circ$ (c = 1, methanol).

[0092] Analogously by reaction of (S)-2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluoro-phenyl)-pyridine (S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane [= (S)-(+)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 227-228°, $[\alpha]^{20}_D = +62^\circ$ (c = 1, methanol).

[0093] Analogously by reaction of (S)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluoro-phenyl)-pyridine:

(S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-8-methoxychromane [= (S)-(+)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 214-215°.

[0094] Analogously by reaction of (R)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluoro-phenyl)-pyridine:

(R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-8-methoxychromane [= (R)-(-)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution

yields the dihydrochloride, m.p. 214°.

Example 20

5 **[0095]** A solution of 5 g (R)-2-aminomethyl-chromane [obtainable by reaction of 2-carboxy-chromane and (+)-phenylethylamine, separation of the mainly crystallising diastereomer purification by recrystallisation from ethanol, transformation into the ethyl chromanate, additional purification via HPLC chiral phases (Chiracel OJ™), transformation into the amide, reduction with LiAlH₄ or Vitride™ in THF to give the (R)-2-aminomethyl-chromane] was reacted with 3-(chloromethyl)-5-phenyl-pyridine analogously to Example 1 to give (R)-(-)-2-[5-phenyl-3-pyridyl-methylaminomethyl]-chromane [= (R)-(-)-1 N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine]. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 243-244°.

[0096] Analogously by reaction of (S)-2-aminomethyl-chromane and 3-(chloromethyl)-5-phenyl-pyridine (S)-(+)-2-(5-phenyl-3-pyridylmethylaminomethyl)-chromane [= (S)-(+)-1 N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 244-245°.

15 **[0097]** Analogously by reaction of (S)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-fluoro-biphenyl: (S)-(+)-2-[4'-fluor-3-biphenyl-yl-methylaminomethyl]-8-methoxy-chromane [= (S)-(+)-1 N-[4'-fluoro-3-biphenyl-yl-methyl]-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 189-190°; [α_D²⁰] = + 74° (c = 1, methanol).

[0098] Analogously by reaction of (R)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-fluoro-biphenyl: (R)-(-)-2-[4'-fluor-3-biphenyl-yl-methylaminomethyl]-8-methoxy-chromane [= (R)-(-)-1 N-[4'-fluoro-3-biphenyl-yl-methyl]-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 189-190°; [α_D²⁰] = - 74,3° (c = 1, methanol).

[0099] The examples below relate to pharmaceutical preparations.

25 Example A: Injection vials

[0100] A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate in 31 of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are closed in a sterile manner. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

35 **[0101]** A mixture of 20 g of active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, and the mixture is poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

40 **[0102]** A solution of 1 g of active compound of the formula I, 9.38 g of NaH₂PO₄ 2H₂O, 28.48 g of Na₂HPO₄ 12H₂O and 0.1 g of benzalkonium chloride is prepared in 940 ml of doubly distilled water. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

45 **[0103]** 500 mg of active compound of the formula I are mixed with 99.5 g of petroleum jell under aseptic conditions.

Example E: Tablets

50 **[0104]** A mixture of 100 g of an active compound of the formula I, 1 kg of lactose, 600 g of microcrystalline cellulose, 600 g of maize starch, 100 g of polyvinyl-pyrrolidone, 80 g of talc and 10 g of magnesium stearate is pressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

55 **[0105]** Tablets are pressed as stated in Example E and then coated in a customary manner with a coating of sucrose, maize starch, talc, tragacanth and colorant.

Example G: Capsules

[0106] Hard gelatin capsules are filled with an active compound of the formula I in the customary manner, so that each capsule contains 5 mg of active compound.

Example H: Inhalation spray

[0107] 14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray burst (about 0.1 ml) corresponds to a dose of about 0.14 mg.

Claims

1. 2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts.
2. Compounds according to Claim 1
 - a) 2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane maleate,
 - b) 2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane dihydrochloride-hemihydrate.
3. S-Enantiomer of the compound according to claim 1 and its physiologically acceptable salts.
4. A process for the preparation of 2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane and its physiologically acceptable salts, characterized in that 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with 2-aminomethyl-chromane, and/or in that the resulting base is converted into one of its salts by treatment with an acid.
5. A process for the preparation of (S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts, characterized in that 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with (S)-2-aminomethyl-chromane, and/or in that the resulting base is converted into one of its salts by treatment with an acid.
6. Process for the manufacture of pharmaceutical preparations, characterised in that a compound according to one or more of claims 1 to 3 and/or one of its biocompatible salts are converted into a suitable dosage form together with at least one solid, liquid or semiliquid excipient or adjunct.
7. Pharmaceutical preparation, characterised in that it contains at least one compound according to one or more of claims 1 to 3 and/or one of its biocompatible salts.
8. Use of compounds according to one or more of claims 1 to 3, or their biocompatible salts, for the manufacture of a drug.
9. Use of compounds according to one or more of claims 1 to 3, or their biocompatible salts, for the manufacture of a pharmaceutical for the treatment of disorders of the central nervous system.
10. Use according to claim 9 in which the disorders of the central nervous system are anxiety, depression states, Alzheimer's disease or schizophrenia.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 10 9746

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DE 42 26 527 A (MERCK PATENT GMBH) 17 February 1994 (1994-02-17) * the whole document *	1,7-10	C07D405/12 C07D311/64 C07D311/58 C07D213/38
A	DE 41 35 474 A (BAYER AG) 29 April 1993 (1993-04-29) * the whole document *	1,7-10	C07D333/20 C07C211/27 A61K31/44 A61K31/35
A	DE 23 64 685 A (BEIERSDORF AG) 3 July 1975 (1975-07-03) * the whole document *	1,7-10	
A	WO 93 17017 A (JANSSEN PHARMACEUTICA N.V.) 2 September 1993 (1993-09-02) * the whole document *	1,7-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D C07C A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 15 June 2001	Examiner Bosma, P
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

EPO FORM 1503 03 82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 10 9746

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-06-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4226527 A	17-02-1994	AU 4456293 A	17-02-1994
		CA 2103601 A	12-02-1994
		CN 1085217 A	13-04-1994
		CZ 9301598 A	16-03-1994
		EP 0586866 A	16-03-1994
		JP 6184140 A	05-07-1994
		MX 9304820 A	28-02-1994
		NO 932842 A	14-02-1994
		PL 300016 A	05-04-1994
		SK 77693 A	11-05-1994
DE 4135474 A	29-04-1993	AT 180777 T	15-06-1999
		AU 2626492 A	29-04-1993
		CA 2081300 A	29-04-1993
		CZ 9203225 A	12-05-1993
		DE 59209704 D	08-07-1999
		EP 0540914 A	12-05-1993
		ES 2132105 T	16-08-1999
		FI 924847 A	29-04-1993
		HU 62875 A	28-06-1993
		JP 5194473 A	03-08-1993
		MX 9205681 A	01-04-1993
		NO 923975 A	29-04-1993
		US 5468882 A	21-11-1995
		US 5962513 A	05-10-1999
		US 5318988 A	07-06-1994
		ZA 9208291 A	06-05-1993
DE 2364685 A	03-07-1975	FR 2255904 A	25-07-1975
		GB 1425150 A	18-02-1976
		JP 50096579 A	31-07-1975
		US 3960878 A	01-06-1976
		US 4005096 A	25-01-1977
		US 4054662 A	18-10-1977
WO 9317017 A	02-09-1993	AP 416 A	29-09-1995
		AT 138064 T	15-06-1996
		AU 3499193 A	13-09-1993
		BG 62052 B	29-01-1999
		BG 98870 A	31-03-1995
		CA 2117483 A	02-09-1993
		CN 1079470 A,B	15-12-1993
		CZ 9402020 A	18-01-1995
		DE 69302687 D	20-06-1996
		DE 69302687 T	14-11-1996
		DK 639192 T	19-08-1996

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 10 9746

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-06-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9317017 A		EP 0639192 A	22-02-1995
		ES 2087721 T	16-07-1996
		FI 943928 A	26-08-1994
		GR 3019927 T	31-08-1996
		HR 930235 A	31-10-1997
		HU 71129 A	28-11-1995
		HU 9500317 A	28-09-1995
		IL 104868 A	04-01-1998
		JP 2779268 B	23-07-1998
		JP 7504408 T	18-05-1995
		KR 190300 B	01-06-1999
		LT 3049 B	25-10-1994
		LV 10715 A	20-06-1995
		LV 10715 B	20-12-1995
		MX 9301053 A	31-03-1994
		NO 943186 A	29-08-1994
		NZ 249124 A	28-08-1995
		OA 10095 A	18-12-1996
		PL 174736 B	30-09-1998
		RO 115630 B	28-04-2000
		RU 2121999 C	20-11-1998
		SG 47763 A	17-04-1998
		SI 9300097 A	30-09-1993
		SK 102994 A	11-07-1995
		US 5541180 A	30-07-1996
		US 5624952 A	29-04-1997
		US 5607949 A	04-03-1997
		US 5688952 A	18-11-1997
		ZA 9301404 A	26-08-1994

EPO FORM P04/99

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 49/04		A1	(11) International Publication Number: WO 95/28969
			(43) International Publication Date: 2 November 1995 (02.11.95)
(21) International Application Number: PCT/GB95/00566		(72) Inventors: RUDDY, Stephen, B. ; 226 Stallion Lane, Schwenksville, PA 19473 (US). MCINTIRE, Gregory, L. ; 113 Piedmont Road, Westchester, PA 19382 (US). ROBERTS, Mary, E. ; 1358 Westminster Drive, Downingtown, PA 19355 (US). TONER, John ; 109 Brookhollow Drive, Downingtown, PA 19355 (US). BACON, Edward, R. ; 1006 Skyline Circle, Audubon, PA 19403 (US). CAULFIELD, Tom ; 2951 Appledale Road, Audubon, PA 19403 (US). COOPER, Eugene, R. ; 2621 Crum Creek Drive, Berwyn, PA 19312 (US). DOUTY, Brent, D. ; Box 475B, Strasburg Road, Coatsville, PA 19320 (US). ILLIG, Carl, R. ; 25 Jonathan Drive, Phoenixville, PA 19460 (US). ESTEP, Kimberly ; 420 Ellis Woods Road, Pottstown, PA 19464 (US).	
(22) International Filing Date: 16 March 1995 (16.03.95)			
(30) Priority Data:			
230,580	21 April 1994 (21.04.94)	US	
236,287	29 April 1994 (29.04.94)	US	
237,502	3 May 1994 (03.05.94)	US	
239,090	5 May 1994 (05.05.94)	US	
247,438	23 May 1994 (23.05.94)	US	
247,424	23 May 1994 (23.05.94)	US	
249,424	26 May 1994 (26.05.94)	US	
(71) Applicant: NYCOMED IMAGING AS [NO/NO] ; Nycoveien 1-2, N-0401 Oslo (NO).		(74) Agent: FRANK B. DEHN & CO. ; Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).	
(71) Applicant (for GB only): MATTHEWS, Derek, Peter [GB/GB] ; 15-19 Kingsway, London WC2B 6UZ (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
		Published <i>With international search report.</i>	
(54) Title: X-RAY CONTRAST COMPOSITIONS CONTAINING PHARMACEUTICALLY ACCEPTABLE CLAYS			
(57) Abstract			
<p>Disclosed are x-ray contrast compositions for oral or retrograde examination of the gastrointestinal tract comprising an x-ray contrast producing agent in combination with a pharmaceutically acceptable clay in a pharmaceutically acceptable carrier, and methods for their use in diagnostic radiology of the gastrointestinal tract.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

X-RAY CONTRAST COMPOSITIONS CONTAINING
PHARMACEUTICALLY ACCEPTABLE CLAYS

This invention relates to an x-ray contrast composition for oral or retrograde administration to a mammal comprising an x-ray contrast producing agent and a pharmaceutically acceptable clay.

Roentgenographic examination utilizing x-rays and computed tomography (hereinafter CT) scans of fractures and other conditions associated with the skeletal system is routinely practiced without the use of contrast agents. X-ray visualization of organs containing soft tissue, such as the gastrointestinal (hereinafter GI) tract, requires the use of contrast agents which attenuate x-ray radiation. D. P. Swanson et al in "Pharmaceuticals In Medical Imaging", 1990, MacMillan Publishing Company, provide an excellent background in medical imaging utilizing contrast agents.

Roentgenographic examination of the GI tract is indicated for conditions of digestive disorders, changes in bowel habit, abdominal pain, GI bleeding and the like. Prior to radiological examination, administration of a radiopaque contrast medium is necessary to permit adequate delineation of the respective lumen or mucosal surface from surrounding soft tissues. Accordingly, a contrast medium is administered orally to visualize the mouth, pharynx, esophagus, stomach, duodenum and proximal small intestine. The contrast medium is administered rectally for examination of the distal small intestine and the colon.

The most widely used contrast agent for the visualization of the GI tract is barium sulfate administered orally as a suspension or rectally as an enema. (See, for example, U.S. Patent Nos.: 2,659,690;

- 2 -

2,680,089; 3,216,900; 3,235,462; 4,038,379 and 4,120,946) Notwithstanding its relatively good contrast characteristics, negligible absorption from the GI tract following oral or rectal administration and speedy excretion from the body, barium sulfate has certain disadvantages. In the presence of intestinal fluids it lacks homogeneity and poorly adheres to mucus membranes which can result in poor x-ray images. In the colon, when administered as an enema, it flocculates and forms irregular clumps with fecal matter.

Iodinated organic compounds have also been used as contrast agents since the iodine atom is an effective x-ray absorber. They have the most versatility and are utilized in the widest variety of procedures. They are very absorptive of x-rays, with which the iodine interacts and produces a so-called photoelectric effect which is a large magnification in contrast caused by the photons stopped in the iodine-containing medium. The magnification of contrast exceeds the level that would be expected from relative changes in density. Because of this magnification, relatively low concentrations of the contrast agent can be utilized. (For iodinated agents see, for example, U.S. Patent Nos.: 2,786,055; 3,795,698; 3,360,436; 3,574,718, 3,733,397; 4,735,795 and 5,047,228.)

The desiderata for an ideal GI contrast agent include: good toxicological profile; the ability to fill the entire bowel/lumen and evenly coat the gut mucosa so that the presence of the bowel is detectable when the lumen is not distended; palatability and nonirritation to the intestinal mucosa; and passing through the GI tract without producing artifacts or stimulating vigorous intestinal peristalsis.

These requirements were addressed by many investigators and their efforts resulted in great improvements over the years. The requirement of evenly coating the gut mucosa with, and sufficiently adhering

- 3 -

thereto, a contrast agent to effectively cover the walls of the intestines proved to be rather difficult. Without meeting these requirements it is impossible to obtain x-ray pictures of high precision. To that end, the use of certain polymer additives were proposed as illustrated hereunder.

U.S. Patent No. 4,069,306 discloses an x-ray contrast preparation which is said to adhere to the walls of body cavities. The preparation comprises a finely divided water-insoluble inorganic x-ray contrast agent and minute particles of a hydrophilic polymer which is insoluble in water but is water-swellable. The body cavity is supplied with such preparation suspended in water. The x-ray contrast agent is present in admixture with and/or enclosed in and/or adhered to said minute polymer particles.

U.S. Patent No. 4,120,946 discloses a pharmaceutical composition for barium opacification of the digestive tract, comprising colloidal barium sulfate and a polyacrylamide in an aqueous vehicle. The polyacrylamide forms a viscous solution at low concentration which makes it possible to maintain the barium sulfate in suspension and at the same time permit good adherence of the preparation to the walls of the organ which it is desired to x-ray.

U.S. Patent No. 5,019,370 discloses a biodegradable radiographic contrast medium comprising biodegradable polymeric spheres which carry a radiographically opaque element, such as iodine, bromine, samarium and erbium. The contrast medium is provided either in a dry or liquid state and may be administered intravenously, orally and intra-arterially.

While these polymeric materials greatly enhance attachment of the contrast agent used therewith to the walls of organs for better visualization thereof, there is still a need for an improved x-ray imaging medium that uniformly coats the soft tissues subjected to

- 4 -

diagnostic x-ray examination.

We have now discovered that the use of certain natural clays in combination with an x-ray producing agent enhances the uniformity of coating on the gastrointestinal tract and the quality of x-ray images. In addition, these clays mask the unpleasant odor and taste of the x-ray contrast formulations as well as enhance the physical stability thereof.

It is the object of the present invention to provide compositions for coating the gastrointestinal tract of mammals to form an effective radiopaque coating thereon by which diagnostic examination of the GI tract may be accomplished. To that end, a thin coating is formed on the inner surface of the GI tract effected by ingesting, prior to visualization by an x-ray emitting device, a composition containing a pharmaceutically acceptable clay and an x-ray contrast agent. Such compositions must meet several requirements: both the x-ray contrast agent and the clay must be nontoxic; must not contain leachable or digestible components that would deleteriously affect the patient; and no components of the coating should be absorbed by, and pass through, the inner surface of the intestine.

The object of the present invention is achieved by a composition comprising: an x-ray contrast agent and a pharmaceutically acceptable clay in an aqueous pharmaceutically acceptable vehicle.

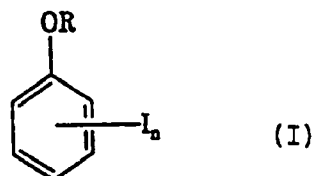
In accordance with the invention there is further provided a method for x-ray diagnostic imaging of the GI tract which comprises orally or rectally administering to the patient an effective contrast producing amount of the above-described x-ray contrast composition.

The contrast agent and the pharmaceutically acceptable clay are incorporated in liquid media for administration to a mammal for x-ray visualization of the GI tract.

- 5 -

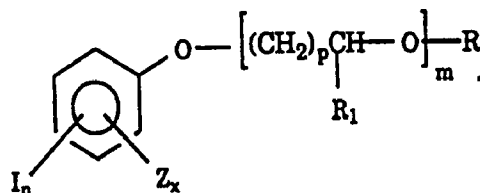
The contrast agents utilized in the present invention are selected from

(1) compounds of the formula (I)



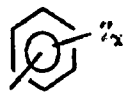
wherein R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C₁-C₆ alkyl, hydroxy and alkoxy; and n is 1 to 5;

(2) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,  or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

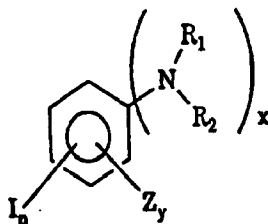
m is 1-15;

p is 1-20; and

- 6 -

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(3) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

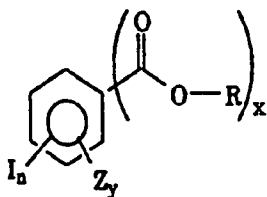
R₁ and R₂ are independently H, C₁-C₂₅ alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C₁-C₂₅ alkyl, cycloalkyl and halo lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

n is 1-4;

y is 1-4; and

x is 1 or 2;

(4) a compound of the formula



wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl,

- 7 -

each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p-(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p-C\equiv C-Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

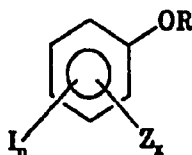
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(5) a compound of the formula



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C_1 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C_9 - C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p-(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p-C\equiv C-Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-5;

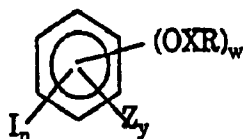
m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

- 8 -

(6) a compound of the formula



wherein

X is O

|
-C- or -SO₂-;

Z is H, halo, methyl, ethyl, n-propyl, C₄-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl or aryl each of which may be optionally substituted with halo, fluoro-lower-alkyl, lower-alkoxy, hydroxy, carboxy or lower-alkoxy carbonyl; lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

n is 1-5;

y is 0-4; and

w is 1-4;

(7) a particulate crystalline x-ray contrast agent having a surface modifier adsorbed on the surface thereof.

As used herein, the term halogen (or halo) means fluorine, chlorine, bromine or iodine.

As used herein, the term cycloalkyl means carbocyclic rings having from three to eight ring carbon atoms including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl which may be substituted on any ring carbon atom thereof by one or more lower-alkyl groups, lower-alkoxy groups or halogens.

As used herein the terms lower-alkyl and lower-alkoxy mean monovalent aliphatic radicals, including

branched chain radicals, of from one to ten carbon atoms. Thus, the lower-alkyl moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein, the terms lower-alkenyl and lower-alkynyl means monovalent, unsaturated radicals including branched chain radicals of from three to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butynyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl) and the like.

As used herein, the term alkylene means divalent saturated radicals, including branched chain radicals of from two to ten carbon atoms having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like.

As used herein, the term aryl means an aromatic hydrocarbon radical having six to ten carbon atoms. The preferred aryl groups are phenyl, substituted phenyl and naphthyl substituted by from one to three, the same or different members of the group consisting of lower-alkyl, halogen, hydroxy-lower-alkyl, alkoxy-lower-alkyl and hydroxy.

The x-ray contrast compounds can comprise one, two, three or more iodine atoms per molecule; preferred species contain at least two, and more preferably, at least three iodine atoms per molecule.

Solid x-ray contrast agents in particulate forms useful in the practice of the present invention can be prepared by techniques known in the art. The solid agents are comminuted to the desired size using

- 10 -

conventional milling methods, such as airjet or fragmentation milling. We have found that an effective average particle size of less than about 100μ provides for good distribution and coating in the GI tract. As used herein, particle size refers to a number average particle size as measured by conventional techniques, such as sedimentation field flow fractionation and disk centrifugation. An effective average particle size of less than about 100μ means that at least about 90% of the particles have a weight average particle size of less than about 100μ as measured by art recognized techniques.

The compositions may be in the form of dispersions, suspensions when the x-ray contrast agent is a solid, or emulsions when the x-ray contrast agent is an oil; we prefer to use emulsions as the preferred embodiment.

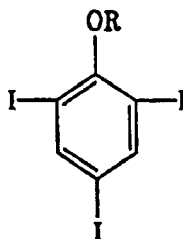
The natural clays incorporated in the compositions of the present invention are selected from the group consisting of montmorillonite, beidelite, nontronite, hectorite and saponite.

A method for diagnostic imaging of the GI tract for use in medical procedures in accordance with this invention comprises orally or rectally administering to the mammalian patient in need of an x-ray examination, an effective contrast producing amount of a composition of the present invention. After administration at least a portion of the GI tract containing the administered composition is exposed to x-rays to produce an x-ray image pattern corresponding to the presence of the contrast agent, then the x-ray image is visualized and interpreted using techniques known in the art.

Compounds of type (1) defined above are described in EP-A-568155. For example, 2,4,6-triiodophenoxy-2-octane, 2,4,6-triiodophenoxy-2-butane, 2,4,6-triiodophenoxy-2-hexane and 4-iodophenoxy-2-octane are described therein.

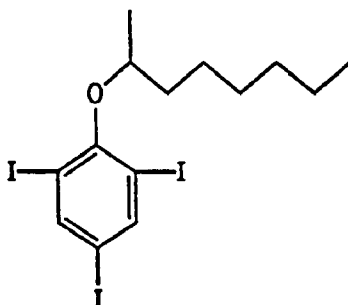
- 11 -

Preferred contrast agents of type (1) have the formula:



wherein R is a secondary alkyl group containing from 4 to 8 carbon atoms.

The most preferred contrast agent of type (1) is the sec-octyl ether of 2,4,6-triiodophenol having the formula:



Compounds of type (2) defined above are described in EP-A-614670. For example, the bis-(4-iodophenyl) ether of polyethylene-glycol-400, 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol, 1,11-bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane, 1,2-bis-(2,4,6-triiodophenoxy)-ethane, the bis-O-(2,4,6-triiodophenyl) ether of polyethylene glycol 400, 1-(3-iodophenoxy)-3,6,9-trioxadecane, 1,3-bis-(2,4,6-triiodophenoxy)-butane, 1-(3-iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane and 1,12-bis-(2,4,6-triiodophenoxy)-dodecane are described therein.

Compounds of type (3) as defined above are described in EP-A-613689. For example, N-acetyl-N-2-octyl-4-iodoaniline and N-(4'-iodophenyl)-2-amino-octane are described therein.

- 12 -

Compounds of type (4) as defined above are described in EP-A-614669. For example, 2-octyl 2,3,5-triiodobenzoate, 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-2-octyl 2,3,5-triiodobenzoate, bis (2-hexyl) 2,3,5,6-tetraiodoterephthalate, ethyl 3-(2-octyloxy)-2,4,6-triiodobenzoate and bis(2-octyl) 5-(2-octyloxy)-2,4,6-triiodoisophthalate are described therein.

Compounds of type (5) as defined above are described in EP-A-609587. For example, 2-(4-iodophenoxy)-decane, 2-(2,4,6-triiodophenoxy)-pentadecane, 2-(2,4,6-triiodophenoxy)decane, (2,4,6-triiodophenoxy)-1H,1H,2H,2H-perfluorooctane, 1-(2,4,6-triiodo-3-trifluorophenoxy)octane, 2-(2,4,6-triiodophenoxy)-nonane, 2-ethyl-1-(2,4,6-triiodophenoxy)-hexane, 3,3-diphenyl-1-(2,4,6-triiodophenoxy)propane, 3-(2,4,6-triiodophenoxy)-nonane, 2-(4-iodophenoxy)-undecane, 2-iodophenoxy cyclopentane, 3-iodophenoxy cyclopentane, (3,5-dimethyl-2,4,6-triiodophenoxy) cyclopentane, 2-(4-iodophenoxy)-pentadecane, 4-iodophenoxy cyclopentane, 2,4,6-triiodophenoxy cyclopentane, 2,4,6-triiodophenoxy methyl cyclopentane, 2-(2,4,6-triiodophenoxy) ethyl cyclopentane, (E,E)-1-(2,4,6-triiodophenoxy)-3,7,11-trimethyl-2,6,10-dodecatriene, 1-(2,4,6-triiodophenoxy)-3,7-dimethyl-6-octene, (E)-1-(3,5-dimethyl-2,4,6-triiodophenoxy)-3,7-dimethyl-2,6-octadiene, (E)-1-(2,4,6-triiodophenoxy)-3,7-dimethyl-2,6-octadiene, 1-(2,4,6-triiodophenoxy)-3-octyne, 2-(2,4,6-triiodophenoxy)-4-octyne, 1-(2,4,6-triiodophenoxy)-3-octyne, diethyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, diisopropyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, ethyl 2,2-bis-(3-iodophenoxy)acetate, ethyl 5-(2,4,6-triiodophenoxy)hexanoate, 5-(2,4,6-triiodophenoxy)-hexan-1-ol, 10-(4-iodophenoxy)-undecan-1-ol, ethyl 5-(2,4,6-triiodophenoxy) hexyl carbonate and ethyl 10-(3-

- 13 -

iodophenoxy)-undecanoate are described therein.

Compounds of type (6) as defined above are described in EP-617970. For example, 2,4,6-triiodophenyl 2-ethylhexanoate, 2,4,6-triiodophenyl 2-methylpentanoate, 2,4,6-triiodophenyl 3-cyclopentyl propionate, 2,4,6-triiodophenyl (2-propyl)pentanoate, 2,4,6-triiodophenyl perfluoroheptanoate, 2,4,6-triiodophenyl-tris-(2-ethyl)-hexanoate, 2,4,6-triiodophenyl dodecanoate, 3-trifluoromethyl-2,4,6-triiodophenyl 2-ethyl hexanoate, 2,4,6-triiodophenyl-bis-(2-methylpentanoate), 2,4,6-triiodophenyl hexanesulfonate, 2,4,6-triiodophenyl heptanesulfonate and 2,4,6-triiodophenyl decanesulfonate are described therein.

Compounds used in the compositions of type (7) defined above are non-radioactive and exist as a discrete, crystalline phase of an organic substance. The crystalline phase differs from an amorphous or non-crystalline phase which results from solvent precipitation techniques such as described in U.S. Patent 4,826,689 noted above. The organic substance can be present in one or more suitable crystalline phases. The invention can be practiced with a wide variety of crystalline, non-radioactive x-ray contrast agents. However, the x-ray contrast agent must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble", it is meant that the agent has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. The preferred liquid dispersion medium is water. Additionally, the invention can be practiced with other liquid media in which the selected x-ray contrast agent is poorly soluble and dispersible, including, for example, aqueous saline solutions, such as phosphate buffered saline (PBS), plasma, mixed

- 14 -

aqueous and nonaqueous solutions, for example, water and alcohol, and suitable nonaqueous solvents such as alcohol, glycerol and the like.

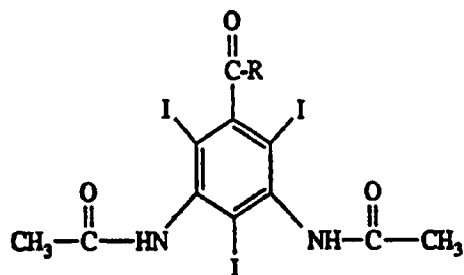
The x-ray contrast agent can be an iodinated compound. The iodinated compound can be aromatic or nonaromatic. Aromatic compounds are preferred. The iodinated compound can comprise, one, two, three or more iodine atoms per molecule. Preferred species contain at least two, and more preferably, at least three iodine atoms per molecule. The iodinated compounds selected can contain substituents that do not impart solubility to the compound, such as, for example, alkylureido, alkoxyacylamido, hydroxyacetamido, butyrolactamido, succinimido, trifluoroacetamido, carboxy, carboxamido, hydroxy, alkoxy, acylamino, and the like substituents.

A preferred class of contrast agents includes various esters and amides of iodinated aromatic acids. The esters preferably are alkyl or substituted alkyl esters. The amides can be primary or secondary amides, preferably alkyl or substituted alkyl amides. For example, the contrast agent can be an ester or amide of a substituted triiodobenzoic acid such as an acyl, carbamyl, and/or acylmethyl substituted triiodobenzoic acid. Illustrative representative examples of iodinated aromatic acids include, but are not limited to, diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxaglic acid (hexabrix), ioxitalamic acid, tetraiodoterephthalic acid, iodipamide, icarmic acid, and the like.

Many of the iodinated molecules described above, if in monomeric form, can also be prepared as dimers (sometimes referred to as bis compounds), trimers (sometimes referred to as tris compounds), etc., by techniques known in the art. It is contemplated that this invention can be practiced with poorly soluble-iodinated compounds in monomeric, dimeric, trimeric and polymeric forms.

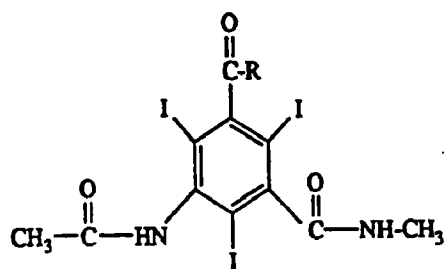
Classes of preferred contrast agents have the following structural formulae:

A.



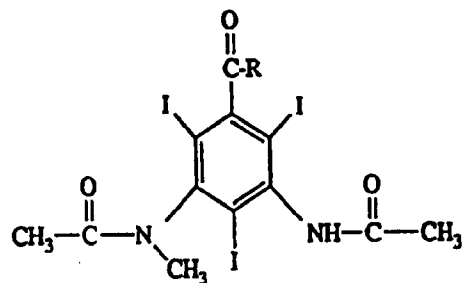
[diatrizoate]

B.

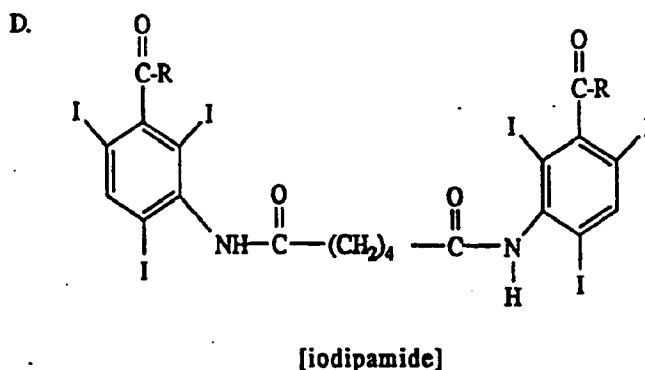


[iothalamate]

C.



- 16 -



In the above structures R can be OR^1 , NR^2R^3 , alkylene, $-CO. OR^1$ or $-O\text{-alkylene-CO}. OR^1$ wherein R^1 is alkyl, and R^2 and R^3 are independently H or alkyl.

Each alkyl group can independently contain from 1-20, preferably 1-8, and more preferably, 1-4 carbon atoms.

The alkylene group preferably contains from 1 to 4 carbon atoms such as methylene, ethylene, propylene and the like.

Particularly preferred contrast agents include the ethyl ester of diatrizoic acid, i.e., ethyl 3,5-diacetamido-2,4,6-triiodobenzoate, also known as ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate or ethyl diatrizoate, having the structural formula A above wherein $R = -OCH_2CH_3$; the ethyl glycolate ester of diatrizoic acid, i.e., ethyl (3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)acetate, also known as ethyl diatrizoxyacetate; and ethyl 2-(3,5-bis(acetylamino)-2,4,6-tri-iodobenzoyloxy)butyrate, also known as ethyl 2-diatrizoxybutyrate.

In addition, the invention can be practiced in conjunction with the water insoluble iodinated carbonate esters described in PCT/EP90/00053.

The above described x-ray contrast agents are known compounds and/or can be prepared by techniques known in the art. For example, water-insoluble esters and

- 17 -

terminal amides of acids such as the above-described iodinated aromatic acids can be prepared by conventional alkylation or amidation techniques known in the art. The above-noted acids and other acids which can be used as starting materials are commercially available and/or can be prepared by techniques known in the art.

The particles useful in the contrast agents of type (7) include a surface modifier. Surface modifiers useful herein physically adhere to the surface of the x-ray contrast agent but do not chemically react with the agent or itself. Individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. Suitable surface modifiers can be selected from known organic and inorganic pharmaceutical excipients such as various polymers, low-molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of surface modifiers include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the

- 18 -

American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxamers such as Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, and poloxamines such as Tetronic 908 (also known as Poloxamine 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 80, which is a polyoxyethylene sorbitan fatty acid ester, available from ICI Specialty Chemicals, and Carbowax 3350 and 934, which are polyethylene glycols available from Union Carbide. Surface modifiers which have been found to be particularly useful include Tetronic 908, the Tweens, Pluronic F-68 and polyvinylpyrrolidone.

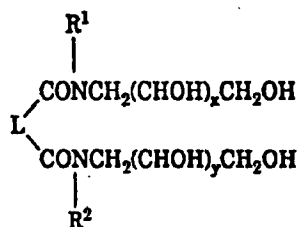
Other useful surface modifiers include:

- decanoyl-N-methylglucamide;
- n-decyl β -D-glucopyranoside;
- n-decyl β -D-maltopyranoside;
- n-dodecyl β -D-glucopyranoside;
- n-dodecyl β -D-maltoside;
- heptanoyl-N-methylglucamide
- n-heptyl β -D-glucopyranoside;
- n-heptyl β -D-thioglucoside;
- n-hexyl β -D-glucopyranoside;
- nonanoyl-N-methylglucamide;

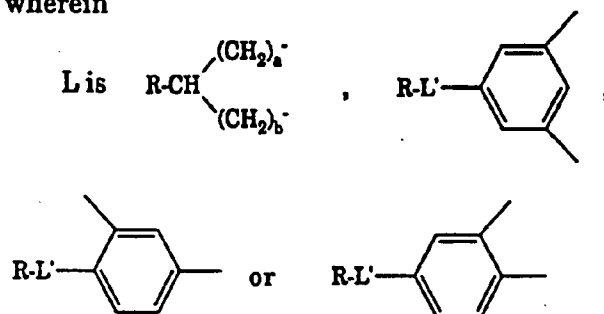
- 19 -

n-nonyl β -D-glucopyranoside;
 octanoyl-N-methylglucamide;
 n-octyl β -D-glucopyranoside;
 octyl β -D-thiogluconopyranoside;
 and the like.

A particularly preferred class of surface modifiers includes water-soluble or water-dispersible compounds having the formula



wherein



L' is a chemical bond, -O-, -S-, -NH-, -CONH- or -SO₂NH-;

R is a hydrophobic substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted aryl group;

each of R¹ and R² independently is hydrogen or an alkyl group having from 1 to 4 carbon atoms;

each of a and b independently is 0 or an integer from 1 to 3, provided that the sum of a and b is not greater than 3; and,

- 20 -

each of x and y independently is an integer from 3 to 7.

Preferred compounds within this class conform to the above structure wherein R contains from 6 to 36 carbon atoms, for example, R is an n-alkyl group containing from 6 to 18 carbon atoms, each of R^1 and R^2 independently is a methyl, ethyl, propyl or butyl group and a is 0 and b is 0. This class of surface modifiers is described in U.K. Patent Application No. 9104957.7 filed March 8, 1991 and can be prepared by reacting an appropriate dicarboxylic acid ester with an appropriate monosaccharide amine, preferably in the absence of a solvent, at a reaction temperature from 140 to 200°C.

The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

The particles can be prepared in accordance with the wet grinding process described in U.S. Patent No. 5,145,684. The process comprises dispersing a poorly soluble x-ray contrast agent in a liquid dispersion medium and wet-grinding the agent in the presence of grinding media to reduce the particle size of the contrast agent to an effective average particle size of from about 0.05 μ to about 100 μ , preferably of from about 0.05 μ to about 5 μ and most preferably from about 0.1 μ to about 1 μ . The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size

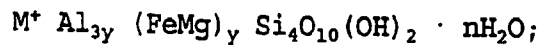
- 21 -

of from about 0.05μ to about 100μ is meant that at least 90% of the particles have a weight average particle size of from about 0.05μ to about 100μ when measured by the above-noted techniques. The particle size range allows sufficient number of particles' distribution in the film forming composition when the GI tract is coated therewith, yet insures against absorption through the intestinal walls.

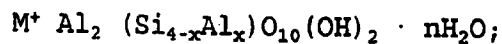
The natural, pharmaceutically acceptable clays incorporated in the present invention comprise aluminum silicates. They are used in purified form, suitable for administration to patients. The natural, pharmaceutically acceptable clays of the present invention, generally referred to as smectites, consist of dioctahedral smectites and trioctahedral smectites.

Dioctahedral smectites include:

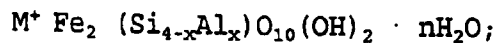
montmorillonite, having the formula



beidelite, having the formula



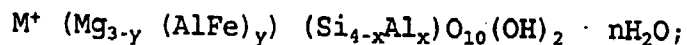
nontronite, having the formula



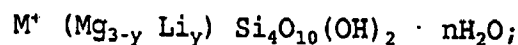
wherein M^+ is Na, Ca or Mg.

Trioctahedral smectites include:

saponite, having the formula



hectorite, having the formula



- 22 -

wherein M^+ is Na, Ca or Mg.

The clays are available from chemical suppliers, such as, for example, American Colloid Company, Arlington Heights, IL, under the tradenames:

MAGNABRITE®HS;
HECTABRITE®DP,
HECTABRITE®LT,
CARMARGO®White,
POLARGEL®NF,
POLARGEL®HV, and
VOLCLAY®NF-BC.

Other suppliers include: Engelhard Corp., Iselin, NJ; Ashland Chemical Inc., Columbus, OH; RT Vanderbilt Co., Inc., Norwalk, CT and Whittaker Clark & Daniels, Inc., S. Plainfield, NJ.

The contrast agent and the pharmaceutically acceptable clay are formulated for administration using physiologically acceptable carriers or excipients in a manner within the skill of the art. The contrast agent with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients may be suspended or emulsified in an aqueous medium resulting in a suspension or emulsion.

Compositions of the present invention comprise the following pharmaceutically acceptable components based on % w/v:

- 23 -

<u>Ingredients</u>	<u>Broad Range</u>	<u>Preferred Range</u>	Most
			<u>Preferred Range</u>
Contrast agent	5 - 45	10 - 35	15 - 25
Clay	0.1 - 10	0.5 - 5	1 - 2
Surfactant	1 - 20	2 - 10	3 - 5
Excipients	0 - 15	0.5 - 5	1 - 2

Water - q.s. to 100% by volume

Excipients contemplated by the present invention include antifoaming agents, such as simethicone, siloxyalkylene polymers and polyoxyalkylated natural oils; preservatives, such as methyl paraben, propyl paraben, benzoic acid and sorbic acid; flavoring/sweetening agents, such as sodium saccharine; and coloring agents, such as lakes and dyes.

While the iodophenoxyalkanes of the present invention in formulations with a pharmaceutically acceptable vehicle provide good quality x-ray images, the addition of a pharmaceutically acceptable clay to the formulations greatly increases the quality of the x-ray images. At the low extreme of the concentration range there is little or no benefit gained, while above the higher extreme of the concentration range the formulation is too viscous for administration.

The following formulation examples will further illustrate the invention.

Example 1

Components

2,4,6-triiodophenoxy-2-butane	20.0 g
HECTABRITE® DP	1.45 g
Sorbitan monostearate	0.5 g
Polysorbate 60	1.0 g
Poloxamer 338	5.0 g

- 24 -

Sodium Saccharine	0.25 g
Benzoic acid	0.50 g
Sorbic Acid	0.050 g
Water q.s. to make 100 ml	

Example 2Components

4-Iodophenoxy-2-octane	22.5 g
POLARGEL® NF	2.25 g
Sorbitan mono-oleate	0.40 g
Polysorbate 20	1.25 g
Polyvinyl alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 3Components

2,4,6-triiodophenoxy-2-hexane	18.5 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.6 g
Polyoxyethylene myristyl ether	0.6 g
Polyvinylpyrrolidone	3.5 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.0 g
Water q.s. to make 100 ml	

Example 4ComponentsAmounts in % w/v

Bis-(4-iodophenyl) ether of polyethylene glycol-400	17.50
HECTABRITE® DP	1.35
Polysorbate 80 (Tween 80)	1.50

- 25 -

Sorbitan Mono-oleate (Span 80) 1.65
q.s. with water to 100% by volume

Example 5

<u>Components</u>	<u>Amounts in % w/v</u>
1,8-Bis-O-(2,4,6-triiodophenyl)- tripropylene glycol	25.00
POLARGEL [®] NF	2.30
Polysorbate 60 (Tween 60)	1.00
Poloxamer 338	6.50
Benzoic Acid	0.50
Sorbic Acid	0.05
q.s. with water to 100% by volume	

Example 6

<u>Components</u>	<u>Amounts in % w/v</u>
1,11-Bis-(2,4,6-triiodophenoxy)- 3,6,9-trioxaundecane	17.50
MAGNABRITE [®] HS	1.25
Polysorbate 20 (Tween 20)	1.50
Sorbitan Mono-laurate (Span 20)	2.00
Polyvinyl Alcohol	4.00
Sodium Saccharin	0.30
q.s. with water to 100% by volume	

Example 7

<u>Components</u>	
N-acetyl-N-2-octyl-4-iodoaniline	18.00 g
HECTABRITE [®] DP	1.5 g
Sorbitan Monostearate	0.5 g
Polysorbate 60 (Tween 60)	1.2 g
Poloxamer 338	4.0 g
Sodium Saccharine	0.3 g
Benzoic Acid	0.1 g

- 26 -

Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 8Components

N-(4'-iodophenyl)-2-amino octane	25.00
POLARGEL® NF	2.0 g
Sorbitan Mono-oleate	0.4 g
Polysorbate 20 (Tween 20)	1.2 g
Polvinylalcohol	4.5 g
Sodium Saccharine	0.2 g
Simethicone (food-grade)	0.1 g
Water q.s. to make 100 ml	

Example 9Components

2-Octyl-2,3,5-triiodobenzoate	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 10Components

3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluoro- 2-octyl-2,3,5-triiodobenzoate	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g

- 27 -

Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 11Components

Ethyl-3-(2-acetyloxy)-2,4,6-triiodobenzoate	18.50g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 12Components

2,4,6-Triiodophenoxymethylcyclopentane	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 13Components

2-(4-Iodophenoxy)pentadecane	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g

- 28 -

Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 14Components

2-Iodophenoxycyclopentane	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	1.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 15Components

2,4,6-Triiodophenyl-2-ethylhexanoate	22.00 g
HECTABRITE®DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

Example 16Components

2,4,6-Triiodophenyl-tris- (2-ethylhexanoate)	22.50 g
POLARGEL®NF	2.30 g

- 29 -

Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 17Components

2,4,6-Triiodophenyl hexanesulfonate	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

Example 18Components

Ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate	22.00 g
HECTABRITE® DP	1.50 g
Sorbitan Monostearate	0.70 g
Polysorbate 60 (Tween 60)	1.20 g
Poloxamer 338	4.00 g
Sodium Saccharine	0.30 g
Benzoic Acid	0.50 g
Sorbic Acid	0.05 g
Water q.s. to make 100 ml	

- 30 -

Example 19Components

Ethyl (3,5-bis(acetylamino)-2,4,6-triiodobenzoxy) acetate	22.50 g
POLARGEL®NF	2.30 g
Sorbitan Mono-oleate	0.45 g
Polysorbate 20 (Tween 820)	1.30 g
Polyvinyl Alcohol	4.50 g
Sodium Saccharine	0.25 g
Simethicone emulsion (food-grade)	0.10 g
Water q.s. to make 100 ml	

Example 20Components

Ethyl 2-(3,5-bis(acetylamino)-2,4,6-triiodobenzoxy) butyrate	18.50 g
MAGNABRITE® HS	1.25 g
Sorbitan monopalmitate	0.60 g
Polyoxyethylene myristyl ether	0.60 g
Polyvinylpyrrolidone	3.50 g
Vanilla flavoring (artificial)	0.25 g
Strawberry flavoring (artificial)	0.25 g
Sorbitol	1.00 g
Water q.s. to make 100 ml	

The surface active agents used in the present invention may be cationic, anionic, nonionic or zwitterionic.

Suitable cationic surfactants include cetyl trimethyl ammonium bromide, cetyl pyridinium chloride, myristyl gamma picolinium chloride and benzalkonium chloride. Suitable anionic agents include sodium lauryl sulphate, sodium heptadecyl sulphate, alkyl benzenesulphonic acids and salts thereof, sodium

butyl-naphthalene sulfonate, and sulphosuccinates. Zwitterionic surface active agents are substances that when dissolved in water they behave as diprotic acids and, as they ionize, they behave both as a weak base and a weak acid. Since the two charges on the molecule balance each other out they act as neutral molecules. The pH at which the zwitterion concentration is maximum is known as the isoelectric point. Compounds, such as certain amino acids having an isoelectric point at the desired pH of the formulations of the present invention are useful in practicing the present invention.

In preparing the formulations of the present invention we prefer to use nonionic emulsifiers or surface active agents which, similarly to the nonionic contrast agents, possess a superior toxicological profile to that of anionic, cationic or zwitterionic agents. In the nonionic emulsifying agents the proportions of hydrophilic and hydrophobic groups are about evenly balanced. They differ from anionic and cationic surfactants by the absence of charge on the molecule and, for that reason, are generally less irritating than the cationic or anionic surfactants. Nonionic surfactants include carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer or ethylene oxide/propylene oxide co-polymers polyvinylpyrrolidone and polyvinylalcohol.

One particular type of carboxylic ester nonionic surface active agents are the partial, for example mono-, esters formed by the reaction of fatty and resin acids, for example of about 8 to about 18 carbon atoms, with polyalcohols, for example glycerol, glycols such as mono-, di-, tetra- and hexaethylene glycol, sorbitan, and the like; and similar compounds formed by the direct addition of varying molar ratios of ethylene oxide to the hydroxy group of fatty acids.

- 32 -

Another type of carboxylic esters are the condensation products of fatty and resin partial acids, for example mono-, esters ethylene oxide, such as fatty or resin acid esters of polyoxyethylene sorbitan and sorbitol, for example polyoxyethylene sorbitan, mono-tall oil esters. These may contain, for example, from about 3 to about 80 oxyethylene units per molecule and fatty or resin acid groups of from about 8 to about 18 carbon atoms. Examples of naturally occurring fatty acid mixtures which may be used are those from coconut oil and tallow while examples of single fatty acids are dodecanoic acid and oleic acid.

Carboxylic amide nonionic surface active agents are the ammonia, monoethylamine and diethylamine amides of fatty acids having an acyl chain of from about 8 to about 18 carbon atoms.

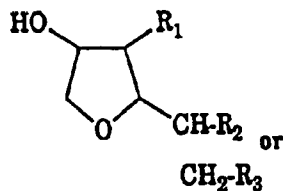
The ethoxylated alkylphenol nonionic surface active agents include various polyethylene oxide condensates of alkylphenols, especially the condensation products of mono-alkylphenols or dialkylphenols wherein the alkyl group contains about 6 to about 12 carbon atoms in either branched chain or particularly straight chain configuration, for example, octyl cresol, octyl phenol or nonyl phenol, with ethylene oxide, said ethylene oxide being present in amounts equal to from about 5 to about 25 moles of ethylene oxide per mole of alkylphenol.

Ethoxylated aliphatic alcohol nonionic surface active agents include the condensation products of aliphatic alcohols having from about 8 to 18 carbon atoms in either straight chain or branched chain configuration, for example oleyl or cetyl alcohol, with ethylene oxide, said ethylene oxide being present in equal amounts from about 30 to about 60 moles of ethylene oxide per mole of alcohol.

Preferred nonionic surface active agents include:

- 33 -

(a) Sorbitan esters (sold under the trade name Span) having the formula:



wherein

$R_1 = R_2 = \text{OH}$, $R_3 = \text{R}$ for sorbitan monoesters,

$R_1 = \text{OH}$, $R_2 = R_3 = \text{R}$ for sorbitan diesters,

$R_1 = R_2 = R_3 = \text{R}$ for sorbitan triesters,

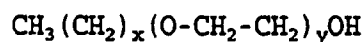
where $\text{R} = (\text{C}_{11}\text{H}_{23})\text{COO}$ for laurate,

$(\text{C}_{17}\text{H}_{33})\text{COO}$ for oleate,

$(\text{C}_{15}\text{H}_{31})\text{COO}$ for palmitate,

$(\text{C}_{17}\text{H}_{35})\text{COO}$ for stearate;

(b) Polyoxyethylene alkyl ethers (i.e. Brij's) having the formula:



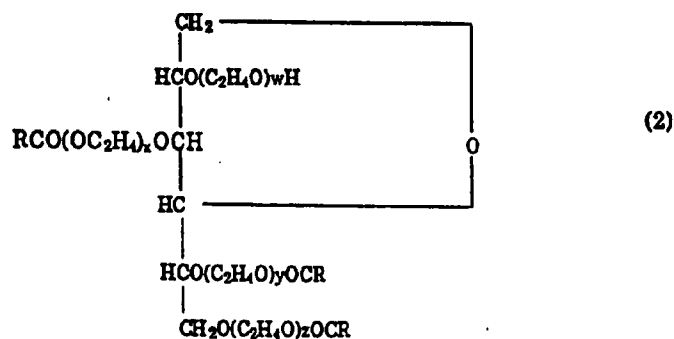
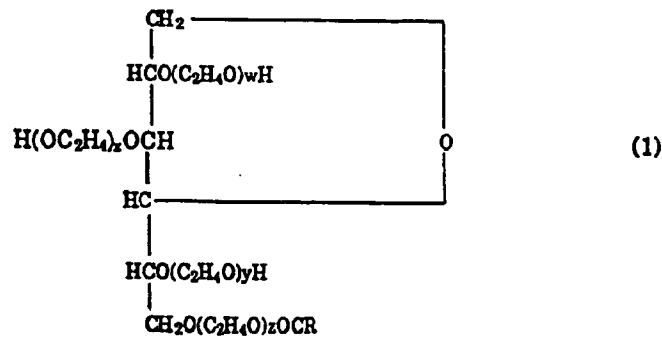
where $(x + 1)$ is the number of carbon atoms in the alkyl chain, typically:

12	lauryl	(dodecyl)
14	myristyl	(tetradecyl)
16	cetyl	(hexadecyl)
18	stearyl	(octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60;

(c) Polyoxyethylene sorbitan fatty acid esters, sold under the trade names of Tween or Polysorbates 20, 40, 60, 65, 80 & 85 having the formulae (1) and (2)

- 34 -



wherein

- $w+x+y+z = 20$ (Polysorbate 20, 40, 60, 65, 80 and 85)
 $w+x+y+z = 5$ (Polysorbate 81)
 $w+x+y+z = 4$ (Polysorbate 21 and 61).

(d) Polyoxyethylene stearates, such as:
 poly(oxy-1,2-ethanediyl), α -hydro- ω -hydroxy-octadecanoate;
 polyethylene glycol monostearate; and
 poly(oxy-1,2-ethanediyl)- α -(1-oxooctadecyl)- ω -hydroxy-polyethylene glycol monostearate.

(e) Polyethylene oxide/polypropylene oxide block copolymers, sold under the name PLURONIC™, which include Poloxamer 407 (PLURONIC™ F127), Poloxamer 188 (PLURONIC™ F68), Poloxamer 237 (PLURONIC™ F87) and Poloxamer 338 (PLURONIC™ F108).

- 35 -

(f) Polyvinylpyrrolidone.

(g) Polyvinylalcohol.

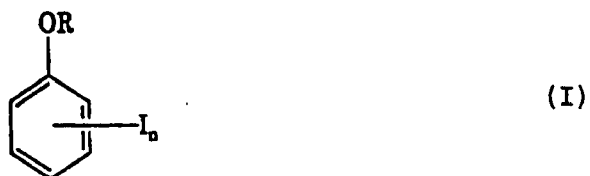
The dosages of the contrast agent used according to the method of the present invention will vary according to the precise nature of the contrast agent used. Preferably, however, the dosage should be kept as low as is consistent with achieving contrast enhanced imaging. By employing as small amount of contrast agent as possible, toxicity potential is minimized. For most contrast agents of the present invention dosages will be in the range of from about 0.1 to about 16.0 g iodine/kg body weight, preferably in the range of from about 0.5 to about 6.0 g iodine/kg of body weight, and most preferably, in the range of from about 1.2 to about 2.0 g iodine/kg body weight for regular x-ray visualization of the GI tract. For CT scanning the contrast agents of the present invention will be in the range of from about 1 to about 600 mg iodine/kg body weight, preferably in the range of from about 20 to about 200 mg iodine/kg body weight, and most preferably in the range of from about 40 to about 80 mg iodine/kg body weight.

When administered to mammals, the compositions of the present invention produce excellent x-ray and CT images.

CLAIMS:

1. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising on a % weight per volume basis:

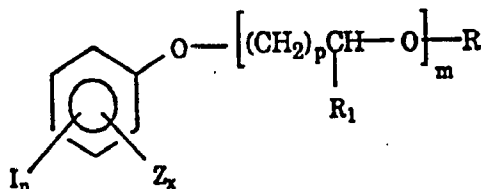
(a) a contrast agent selected from (1) from about 5 to 45% of an x-ray contrast producing agent having the formula



or a pharmaceutically acceptable salt thereof wherein

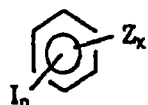
R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C₁-C₆ alkyl, hydroxy and alkoxy; and n is 1 to 5; or

(2) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxycarbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,  or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C=C-Q;

- 37 -

R_1 , R_2 , R_3 and R_4 are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

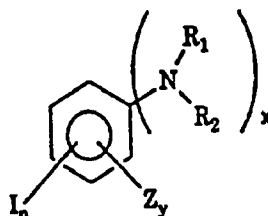
n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(3) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C_1 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R_1 and R_2 are independently H, C_1 - C_{25} alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C_1 - C_{25} alkyl, cycloalkyl and halo lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

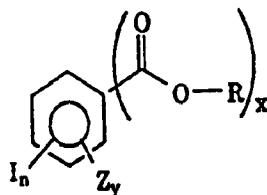
n is 1-4;

y is 1-4; and

x is 1 or 2;

(4) from about 5 to 45% of an x-ray contrast producing agent having the formula

- 38 -



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or (CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

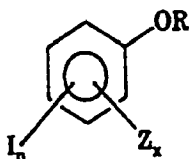
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(5) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C₉-C₂₅ alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted

with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p-(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p-C\equiv C-Q$;

R_1 , R_2 , R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

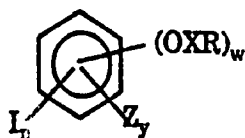
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(6) from about 5 to 45% of an x-ray contrast producing agent having the formula,



or a pharmaceutically acceptable salt thereof wherein

X is $\begin{array}{c} O \\ | \\ -C- \text{ or } -SO_2- \end{array}$;

Z is H, halo, methyl, ethyl, n-propyl, C_4 - C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1 - C_{25} alkyl, cycloalkyl or aryl each of which may be optionally substituted with halo, fluoro-lower-alkyl, lower-alkoxy, hydroxy, carboxy or lower-alkoxy carbonyl; lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

n is 1-5;

y is 0-4; and

w is 1-4;

- 40 -

(7) from about 5 to 45% of a crystalline contrast producing agent selected from the group consisting of diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxathalamic acid, tetraiodoterephthalic acid, ioxaglic acid, iodipamide, ethyl-3,5-diacetamido-2,4,6-triiodobenzoate, ethyl-2-(3,5-bis(acetylamino)-2,4,6-triiodo-benzoyloxy)butyrate, and ethyl(3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)-acetate, said crystalline contrast agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of from about 0.5 μ to about 100 μ ; and

said surface modifier is selected from the group consisting of tetrafunctional block copolymers derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine;

(b) from about 0.1 to 10% of a pharmaceutically acceptable clay selected from the group consisting of: montmorillonite, beidelite, nontronite, hectorite and saponite;

(c) from about 1.0 to 20% of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(d) from about 0 to 15% of an excipient; and

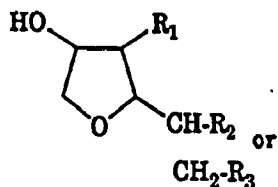
(e) water to make 100% by volume.

2. The x-ray contrast composition of claim 1 wherein said x-ray contrast producing agent is present in an amount of from about 10 to 35%.

3. The x-ray contrast composition of claim 1 wherein said pharmaceutically acceptable clay constitutes from 0.5 to 5% of the composition.

- 41 -

4. The x-ray contrast composition of claim 1 wherein said surfactant constitutes from 2 to 10% of the composition.
5. The x-ray contrast composition of claim 1 wherein said excipient constitutes from 0.5 to 5% of the composition.
6. The x-ray contrast composition of claim 1 wherein said nonionic surface active agent is selected from the group consisting of carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer, ethylene oxide/propylene oxide co-polymer, polyvinylpyrrolidone and polyvinylalcohol.
7. The x-ray contrast composition of claim 1 wherein said surfactant is sorbitan ester having the formula:



wherein

$\text{R}_1 = \text{R}_2 = \text{OH}$, $\text{R}_3 = \text{R}$ for sorbitan monoesters,

$\text{R}_1 = \text{OH}$, $\text{R}_2 = \text{R}_3 = \text{R}$ for sorbitan diesters,

$\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}$ for sorbitan triesters;

where $\text{R} = (\text{C}_{11}\text{H}_{23})\text{COO}$ for laurate,

$(\text{C}_{17}\text{H}_{33})\text{COO}$ for oleate,

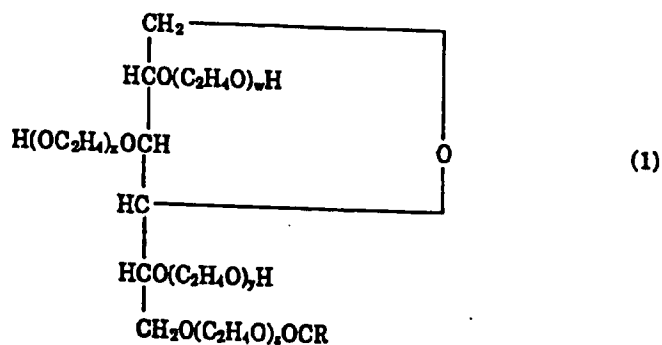
$(\text{C}_{15}\text{H}_{31})\text{COO}$ for palmitate or

$(\text{C}_{17}\text{H}_{35})\text{COO}$ for stearate.

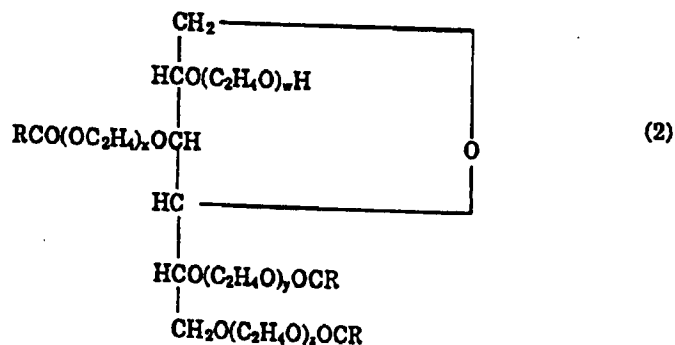
8. The x-ray contrast composition of claim 1 wherein said surface active agent is polyoxyethylene stearate.

9. The x-ray contrast composition of claim 1 wherein said surfactant is polyoxyethylene sorbitan fatty acid

ester of the formulae (1) and (2)



Polyoxyethylene sorbitan monoester



wherein

$$w+x+y+z = 20$$

$$w+x+y+z = 5$$

$$w+x+y+z = 4.$$

10. A method of carrying out x-ray examination of the gastrointestinal tract of a patient, said method comprises the oral or rectal administration to the patient an x-ray contrast formulation of any preceding claim.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/GB 95/00566

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US,A,5 360 604 (STEPHEN B. RUDDY) 1 November 1994 see the whole document ---	1-10
X	GB,A,767 788 (SCHERING CO.) 6 February 1957 see page 5, column 1, line 27 - line 31; claims ---	1
X	CH,A,338 274 (SCHERING CO.) 30 June 1959 see page 2, column 1, line 17 - line 17; claims ---	1
A	FR,A,2 085 692 (E. R. SQUIBB & SONS, INC.) 31 December 1971 see claims 1-3; example 3 ---	1
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 June 1995

Date of mailing of the international search report

25.07.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

BERTE, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00566

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 568 155 (STERLING WINTHROP INC) 3 November 1993 cited in the application see page 6, column 48 - column 58; claims see page 6, column 14 - column 15 see page 7, line 39 - page 8, line 14 ---	1-10
A	EP,A,0 568 156 (STERLING WINTHROP INC) 3 November 1993 see page 3, line 55 - page 5, line 34; claims ---	1-10
P,A	EP,A,0 603 922 (STERLING WINTHROP INC) 29 June 1994 see page 6, line 45 - line 48; claims ---	1-10
P,A	EP,A,0 603 923 (STERLING WINTHROP INC) 29 June 1994 see claims ---	1-10
P,A	EP,A,0 609 589 (STERLING WINTHROP INC) 10 August 1994 see claims ---	1-10
P,A	EP,A,0 614 668 (STERLING WINTHROP INC) 14 September 1994 see page 5, line 28 - page 7, line 29 ---	1-10
P,A	US,A,5 316 755 (ILLIG CARL R ET AL) 31 May 1994 see column 27, line 17 - column 29, line 55; claims ---	1-10
P,A	US,A,5 308 607 (JOSEF KURT A ET AL) 3 May 1994 see column 13, line 47 - column 16, line 9; claims ---	1-10
P,A	US,A,5 310 537 (ILLIG CARL R. ET AL.) 10 May 1994 see column 5, line 51 - column 8, line 18; claims & EP,A,0 613 690 ---	1-10
P,A	US,A,5 310 538 (BACON EDWARD R ET AL) 10 May 1994 cited in the application see column 12, line 65 - column 17, line 4; claims & EP,A,0 614 670 ---	1-10

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00566

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	US,A,5 312 616 (ILLIG CARL R ET AL) 17 May 1994 cited in the application see column 10, line 50 - column 15, line 35; claims & EP,A,0 614 669 ---	1-10
P,A	US,A,5 336 484 (BACON EDWARD R ET AL) 9 August 1994 cited in the application see column 13, line 10 - column 17, line 55; claims & EP,A,0 617 970 ---	1-10
P,A	US,A,5 318 769 (BACON EDWARD R ET AL) 7 June 1994 see column 12, line 1 - column 14, line 35; claims ---	1-10
P,A	US,A,5 326 553 (ILLIG CARL R ET AL) 5 July 1994 cited in the application see column 27, line 17 - column 31, line 59; claims & EP,A,0 609 587 -----	1-10

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5360604	01-11-94	US-A- 5368837	29-11-94
GB-A-767788		NONE	
CH-A-338274		NONE	
FR-A-2085692	31-12-71	CA-A- 985626	16-03-76
		CH-A- 535050	31-03-73
		DE-A- 2110932	23-09-71
		GB-A- 1353635	22-05-74
		US-A- 3984571	05-10-76
EP-A-0568155	03-11-93	AU-B- 3831593	04-11-93
		HU-A- 64700	28-02-94
		JP-A- 6025016	01-02-94
		US-A- 5318768	07-06-94
		US-A- 5342605	30-08-94
		US-A- 5352434	04-10-94
		US-A- 5405600	11-04-95
EP-A-0568156	03-11-93	US-A- 5260049	09-11-93
		AU-B- 3831693	04-11-93
		HU-A- 65306	02-05-94
		JP-A- 6025017	01-02-94
EP-A-0603922	29-06-94	US-A- 5322679	21-06-94
		AU-B- 4737593	30-06-94
		CA-A- 2106413	17-06-94
		CZ-A- 9302748	13-07-94
		FI-A- 935308	17-06-94
		HU-A- 65772	28-07-94
		JP-A- 6199754	19-07-94
		NO-A- 934333	17-06-94
EP-A-0603923	29-06-94	AU-B- 5046793	23-06-94
		CA-A- 2102269	15-06-94
		FI-A- 935307	15-06-94
		HU-A- 66332	28-11-94
		JP-A- 6228068	16-08-94
		NO-A- 934316	15-06-94

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0603923		US-A- 5384107	24-01-95
EP-A-0609589	10-08-94	US-A- 5334370 AU-B- 5047093 CA-A- 2109443 CZ-A- 9400110 FI-A- 940007 JP-A- 6234664 NO-A- 934770	02-08-94 11-08-94 05-08-94 17-08-94 05-08-94 23-08-94 05-08-94
EP-A-0614668	14-09-94	US-A- 5344638 AU-B- 5768194 CA-A- 2116832 HU-A- 66946 JP-A- 6321867	06-09-94 15-09-94 12-09-94 30-01-95 22-11-94
US-A-5316755	31-05-94	AU-B- 4622593 CA-A- 2105729 CZ-A- 9400140 EP-A- 0609586 FI-A- 940006 HU-A- 67315 JP-A- 6234687 NO-A- 934794	04-08-94 03-08-94 17-08-94 10-08-94 03-08-94 28-03-95 23-08-94 03-08-94
US-A-5308607	03-05-94	AU-B- 5046993 CA-A- 2102247 CZ-A- 9400109 EP-A- 0609588 FI-A- 940008 JP-A- 6234673 NO-A- 934795 NZ-A- 250064 US-A- 5385721	11-08-94 05-08-94 17-08-94 10-08-94 05-08-94 23-08-94 05-08-94 25-11-94 31-01-95
US-A-5310537	10-05-94	AU-B- 5644694 CA-A- 2114903 EP-A- 0613690 HU-A- 68191 JP-A- 6298710	08-09-94 02-09-94 07-09-94 29-05-95 25-10-94

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0613690	07-09-94	US-A- 5310537 AU-B- 5644694 CA-A- 2114903 HU-A- 68191 JP-A- 6298710	10-05-94 08-09-94 02-09-94 29-05-95 25-10-94
US-A-5310538	10-05-94	AU-B- 5767994 CA-A- 2115794 EP-A- 0614670 HU-A- 68143 JP-A- 6321814	15-09-94 12-09-94 14-09-94 29-05-95 22-11-94
EP-A-0614670	14-09-94	US-A- 5310538 AU-B- 5767994 CA-A- 2115794 HU-A- 68143 JP-A- 6321814	10-05-94 15-09-94 12-09-94 29-05-95 22-11-94
US-A-5312616	17-05-94	AU-B- 5768294 CA-A- 2116831 EP-A- 0614669 JP-A- 6321813 US-A- 5385720	15-09-94 12-09-94 14-09-94 22-11-94 31-01-95
EP-A-0614669	14-09-94	US-A- 5312616 AU-B- 5768294 CA-A- 2116831 JP-A- 6321813 US-A- 5385720	17-05-94 15-09-94 12-09-94 22-11-94 31-01-95
US-A-5336484	09-08-94	AU-B- 5914694 CA-A- 2115907 EP-A- 0617970 HU-A- 66557 JP-A- 6321815 US-A- 5372800	06-10-94 01-10-94 05-10-94 28-12-94 22-11-94 13-12-94
EP-A-0617970	05-10-94	US-A- 5336484 AU-B- 5914694 CA-A- 2115907	09-08-94 06-10-94 01-10-94

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/GB 95/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0617970		HU-A- 66557	28-12-94
		JP-A- 6321815	22-11-94
		US-A- 5372800	13-12-94

US-A-5318769	07-06-94	AU-B- 5914794	06-10-94
		CA-A- 2115910	01-10-94
		EP-A- 0617969	05-10-94
		JP-A- 6321865	22-11-94
		US-A- 5385722	31-01-95

US-A-5326553	05-07-94	AU-B- 4616193	04-08-94
		CA-A- 2105730	03-08-94
		CZ-A- 9400171	17-08-94
		EP-A- 0609587	10-08-94
		FI-A- 940005	03-08-94
		HU-A- 67347	28-03-95
		JP-A- 6234663	23-08-94
		NO-A- 934793	03-08-94

EP-A-0609587	10-08-94	US-A- 5326553	05-07-94
		AU-B- 4616193	04-08-94
		CA-A- 2105730	03-08-94
		CZ-A- 9400171	17-08-94
		FI-A- 940005	03-08-94
		HU-A- 67347	28-03-95
		JP-A- 6234663	23-08-94
		NO-A- 934793	03-08-94

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/00566

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-2, 4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see enclosure!
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Meaningful search not possible....

II.) Obscurities,...

In view of the definition of products by means of their biological, chemical, and/or pharmacological properties, the search has to be restricted for economic reasons.

The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims or examples. (see guidelines Part B, Chapter III, paragraph 3.6)

特開平8-325154

(43) 公開日 平成8年(1996)12月10日

(51) Int.Cl. ⁶	識別記号	庁内整理番号	F I	技術表示箇所
A 6 1 K 31/60	AED		A 6 1 K 31/60	AED
	ABE			ABE
	ABF			ABF
	ABG			ABG
	ABN			ABN

審査請求 未請求 請求項の数 5 OL (全 16 頁) 最終頁に続く

(21) 出願番号 特願平8-74196

(22) 出願日 平成8年(1996)3月28日

(31) 優先権主張番号 特願平7-76175

(32) 優先日 平7(1995)3月31日

(33) 優先権主張国 日本 (J P)

(31) 優先権主張番号 特願平7-76176

(32) 優先日 平7(1995)3月31日

(33) 優先権主張国 日本 (J P)

(71) 出願人 000003126
三井東圧化学株式会社
東京都千代田区霞が関三丁目2番5号

(72) 発明者 山下 博之
千葉県茂原市東郷1144番地 三井東圧化学株式会社内

(72) 発明者 奥村 邦雄
千葉県茂原市東郷1144番地 三井東圧化学株式会社内

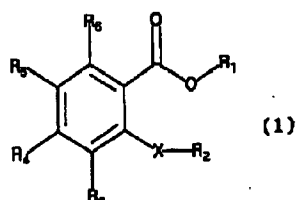
(72) 発明者 溝上 健二
千葉県茂原市東郷1144番地 三井東圧化学株式会社内

最終頁に続く

(54) 【発明の名称】 安息香酸誘導体およびそれを有効成分として含有するホスホリパーゼA₂阻害剤

(57) 【要約】 (修正有) は治療薬として有用である。

【解決手段】 一般式(1)で表される安息香酸誘導体またはその薬理学的に許容される塩、およびそれを有効成分とするPLA₂阻害剤並びに、炎症性疾患の治療および/または予防剤。



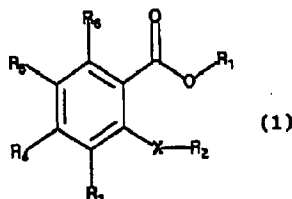
〔式中、R₁は水素原子、低級アルキル基等；R₂はC₁₀〜C₃₀アルキル基；R₃, R₄, R₅, R₆は水素原子、ハロゲン原子、ニトロ基、水酸基、アミノ基等；Xは酸素原子またはイオウ原子；を示す〕

【効果】 一般式(1)で示される安息香酸誘導体は、I型およびII型ホスホリパーゼA₂に対する強い阻害活性を有しており、肺炎、リウマチ、アレルギー、虚血性血管障害、気管支喘息、潰瘍、関節炎、皮膚炎、痛風、外傷誘発炎症などの炎症性疾患の予防および/また

【特許請求の範囲】

【請求項1】 一般式(1)【化1】

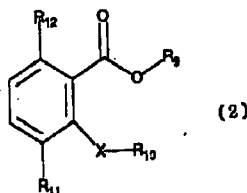
【化1】



(式中、Xは酸素原子またはイオウ原子を、 R_1 は水素原子、低級アルキル基、 $-(CH_2)_n C(=O)O$ (R_7)、 $-(CH_2)_n OC(=O)R_7$ または $-(CH_2)_n N(R_7)$ (R_8)を示し、 R_2 はハロゲン原子、フェニル基、置換フェニル基または水酸基で置換されていてもよく、途中の任意の位置に1個の $-O-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、 $-N(R_7)-$ 、 $-C(=O)-$ 、 $-C(=O)O-$ 、 $-OC(=O)-$ 、 $-C(=O)N(R_7)-$ 、 $-N(R_7)C(=O)-$ 、二重結合、三重結合から選択される結合を有してもよく、直鎖でも環構造でも分枝していてもよい炭素数10から30のアルキル基を示し、 R_3 、 R_4 、 R_5 および R_6 は同一もしくは異なって水素原子、水酸基、ニトロ基、アミノ基、シアノ基、低級アルキルアミノ基、ヒドロキシ低級アルキルアミノ基、低級アルカノイルアミノ基、低級アルカノイルオキシ基、低級アルキルスルホニルアミノ基、低級アルキルスルホニルオキシ基、低級アルコキシ基、ヒドロキシ低級アルコキシ基、低級アルキル基、低級アルカノイル基、カルボキシ基、カルバモイル基、ハロゲン原子またはハロゲン化低級アルキル基を示し、 R_7 および R_8 は同一もしくは異なって水素原子、低級アルキル基または $-CH_2CH_2OH$ を示し、 n は1から6の整数を示す。)で表されることを特徴とする安息香酸誘導体またはその薬理学的に許容される塩を有効成分として含有するホスホリパーゼ A_2 阻害剤。

【請求項2】 一般式(2)【化2】

【化2】



(式中、Xは酸素原子またはイオウ原子を、 R_9 は水素原子、低級アルキル基または $-(CH_2)_n N(R_{13})$ (R_{14})を示し、 R_{10} はハロゲン原子、カルボキシ基、水酸基、フェニル基または置換フェニル基で置換されてもよく、途中の任意の位置に1個の $-O-$ 結合または1個および複数の2重結合を有してもよい炭素数10から30の、直鎖でも分枝していてもよいアルキル基を示し、 R_{11} および R_{12} は同一もしくは異なって水

素原子、ニトロ基、アミノ基、低級アルキルスルホニルアミノ基、水酸基、低級アルコキシ基またはヒドロキシ低級アルコキシ基を示す。 R_{13} および R_{14} は同一のまたは異なって水素原子または低級アルキル基を示す。 n は1から6の整数を表す。ただし、 R_{11} および R_{12} がともに水素原子である場合に R_{10} が炭素数12、14、16または18で無置換の直鎖アルキル基および分枝アルキル基である場合を除く。)で表されることを特徴とする安息香酸誘導体またはその薬理学的に許容される塩。

【請求項3】 一般式(2)のXが酸素原子、 R_{10} が炭素数10から22の直鎖アルキル基、 R_{11} および R_{12} が水素原子である請求項2記載のアルコキシ安息香酸誘導体またはその薬理学的に許容される塩。ただし、 R_{10} が炭素数12、14、16または18である場合は除く。

【請求項4】 請求項1～3のいずれかに記載のホスホリパーゼ A_2 阻害剤を有効成分とする肺炎、リウマチ、アレルギー、虚血性血管障害、気管支喘息、潰瘍、関節炎、皮膚炎、痛風または外傷誘発炎症等の炎症性疾患予防および/または治療薬。

【請求項5】 炎症性疾患が急性または慢性肺炎である請求項4記載の予防および/または治療薬。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は、安息香酸誘導体を有効成分として含有するホスホリパーゼ A_2 (以下、 PLA_2 と略す) 阻害剤に関する。さらに詳しくは、肺炎、リウマチ、アレルギー、虚血性血管障害、気管支喘息、潰瘍、関節炎、皮膚炎、痛風、外傷誘発炎症などの炎症性疾患の予防および/または治療薬として有用な PLA_2 阻害剤に関するものである。

【0002】

【従来の技術】これまで各種炎症性疾患の治療薬としては、ステロイド系薬剤と、非ステロイド系薬剤とが知られている。前者はプロスタグランジン類およびロイコトリエン類の両方の生合成経路を阻害することにより、強い抗炎症作用を示すが、同時に多くの場合、副作用が出現し問題となっている。また後者は前者に比較して、抗炎症作用が弱くさらに有効な薬剤が望まれている。

【0003】一方プロスタグランジン、ロイコトリエンの一連の生体内反応の律速酵素として PLA_2 が注目されている。この PLA_2 の阻害剤はプロスタグランジンとロイコトリエンの両方の生合成を抑えることができ、副作用の少ない強力な抗炎症作用を有する薬剤であると期待されている。 PLA_2 阻害剤の抗炎症作用に関しては既に国内外の数多くの文献に記載されている [Drug of the Future, 15, 140(1990); Arthritis and Rheumatism, 36, 130(1993); Immunology Today, 12(1991)等]。 PLA_2 阻害剤としては、p-ブロモフェナシルプロミド等、種々のものが従来から知られているが、阻

害活性が十分でない等の問題があり、未だ医薬品として上市されたものはない。

【0004】なお、一般式(1)で表される化合物の中には公知化合物が含まれているが、その用途として知られているのは、色素用カップラー原料[CS265355、DE2114577、EP423764、DD255999]、駆虫剤原料[Collect. Czech. Chem. Commun. 41, 3628(1976)]、抗結核菌剤[薬学雑誌, 79, 1378(1959)]などであり、一般式(1)で表される化合物が、PLA₂阻害作用を示すことは全く知られていない。

【0005】

【発明が解決しようとする課題】PLA₂には膵臓から消化酵素として外分泌されるI型と、細胞内に存在しアラキドン酸代謝の初期過程に関与する内分泌性のII型の存在が知られ、通常の炎症ではII型が重要であるとされている。しかし、肺炎では通常の炎症と異なってI型酵素による自己消化がまず問題となり、膵臓から血液中に逸脱したプロテアーゼ、アミラーゼ、リパーゼ、I型PLA₂等が各臓器に働いて炎症を起こし、その部位でII型PLA₂が活性化され、多臓器障害の原因になると考えられている[Scand. J. Gastroent., 15, 519(1980); Digestion, 52, 22(1990); International Journal of Pancreatolgy, 8, 187(1991)]。したがって、肺炎を含む炎症性疾患治療薬に有用であるためには、I型及びII型を共に強く阻害するPLA₂阻害剤が必要であるが、これまでこのような観点からのPLA₂阻害剤の探索は知られていない。すなわち本発明は、I型及びII型を共に強く阻害するPLA₂阻害剤の提供を目的とするものである。

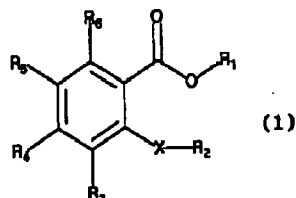
【0006】

【課題を解決するための手段】本発明者は、上記課題を解決するために多くの化合物を合成評価してきた。それらの内、以下に示す安息香酸誘導体が目的とする強いPLA₂阻害活性を有し、かつ肺炎等の炎症性疾患の予防および/または治療薬として有用であることを見だし本発明を完成した。すなわち、本発明は、

[1] 一般式(1)【化3】

【0007】

【化3】



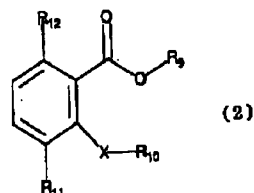
(式中、Xは酸素原子またはイオウ原子を、R₁は水素原子、低級アルキル基、-(CH₂)_nC(=O)O R₇、-(CH₂)_nOC(=O)R₇または-(CH₂)_nN(R₇)(R₈)を示し、R₂はハロゲン原子、フェニル基、置換フェニル基または水酸基で置換されていても

よく、途中の任意の位置に1個の-O-、-S-、-S(O)-、-S(O)₂-、-N(R₇)-、-C(=O)-、-C(=O)O-、-OC(=O)-、-C(=O)N(R₇)-、-N(R₇)C(=O)-、二重結合、三重結合から選択される結合を有してもよく、直鎖でも環構造でも分枝していてもよい炭素数10から30のアルキル基を示し、R₃、R₄、R₅およびR₆は同一もしくは異なって水素原子、水酸基、ニトロ基、アミノ基、シアノ基、低級アルキルアミノ基、ヒドロキシ低級アルキルアミノ基、低級アルカノイルアミノ基、低級アルカノイルオキシ基、低級アルキルスルホニルアミノ基、低級アルキルスルホニルオキシ基、低級アルコキシ基、ヒドロキシ低級アルコキシ基、低級アルキル基、低級アルカノイル基、カルボキシ基、カルボモイル基、ハロゲン原子またはハロゲン化低級アルキル基を示し、R₇およびR₈は同一もしくは異なって水素原子、低級アルキル基または-CH₂CH₂OHを示し、nは1から6の整数を示す。)で表されることを特徴とする安息香酸誘導体またはその薬理的に許容される塩を有効成分として含有するホスホリパーゼA₂阻害剤であり、また、

[2] 一般式(2)【化4】

【0008】

【化4】



(式中、Xは酸素原子またはイオウ原子を、R₉は水素原子、低級アルキル基または-(CH₂)_n-N

(R₁₃)(R₁₄)を示し、R₁₀はハロゲン原子、カルボキシ基、水酸基、フェニル基または置換フェニル基で置換されてもよく、途中の任意の位置に1個の-O-結合または1個および複数の2重結合を有してもよい炭素数10から30の、直鎖でも分枝していてもよいアルキル基を示し、R₁₁およびR₁₂は同一もしくは異なって水素原子、ニトロ基、アミノ基、低級アルキルスルホニルアミノ基、水酸基、低級アルコキシ基またはヒドロキシ低級アルコキシ基を示す。R₁₃およびR₁₄は同一のまたは異なって水素原子または低級アルキル基を示す。nは1から6の整数を表す。ただし、R₁₁およびR₁₂がともに水素原子である場合にR₁₀が炭素数12、14、16または18で無置換の直鎖アルキル基および分枝アルキル基である場合を除く。)で表されることを特徴とする安息香酸誘導体またはその薬理的に許容される塩であり、また、

【0009】[3] 一般式(2)のXが酸素原子、R₁₀が炭素数10から22の直鎖アルキル基、R₁₁および

R_{12} が水素原子である請求項2記載のアルコキシ安息香酸誘導体またはその薬理学的に許容される塩。ただし、 R_{10} が炭素数12、14、16または18である場合は除くであり、また、

【0010】[4] [1]～[3]のいずれかに記載のホスホリパーゼ A_2 阻害剤を有効成分とする肺炎、リウマチ、アレルギー、虚血性血管障害、気管支喘息、潰瘍、関節炎、皮膚炎、痛風または外傷誘発炎症等の炎症性疾患予防および/または治療薬であり、また、

【0011】[5] 炎症性疾患が急性または慢性肺炎である[4]記載の予防および/または治療薬である。

【0012】

【発明の実施の形態】以下、本発明をさらに詳細に説明する。一般式(1)において $-CO_2R_1$ のオルト位に O R_2 基、 SR_2 基が、また一般式(2)において $-CO_2R_9$ のオルト位に OR_{10} 、 SR_{10} 基が存在することが重要であり、メタ位、パラ位に置換基が存在する場合ではI型 PLA_2 に対する阻害活性は低い。

【0013】 R_2 、 R_{10} の炭素数は10から30であり、好ましくは炭素数が10から22である。炭素数10未満の場合にはI型、II型 PLA_2 に対する阻害活性が著しく低下し、炭素数が30を越えればI型 PLA_2 に対する阻害活性低下が認められる。また、 R_2 はハロゲン原子または水酸基で置換されていてもよいが、水酸基の場合は2個以下が好ましい。さらに、 R_2 はその置換基の任意の位置にエーテル結合などを1個有してもよいが、2個以上の存在は活性低下を示す。 R_4 、 R_5 は共に水素原子であるものが好ましく、さらには R_3 、 R_6 が同一もしくは異なって水素原子、水酸基またはニトロ基であるものが好ましい。

【0014】in vitroでの PLA_2 阻害活性本体は、一般式(1)または(2)の R_1 または R_9 が水素原子のカルボン酸化合物およびその塩であるが、吸収率改善、作用持続時間の延長、毒性の低減、水溶性の改善、物性の改善などを目的に、従来技術によりプロドラッグ体として使用することもでき、 R_1 として水素原子の他、低級アルキル基、 $-(CH_2)_nC(=O)OR_7$ 、 $-(CH_2)_nOC(=O)R_7$ あるいは $-(CH_2)_nN(R_7)(R_8)$ を、 R_9 としては水素原子の他、低級アルキル基または $-(CH_2)_nN(R_{13})(R_{14})$ などの形態をとることができる。

【0015】一般式(1)または(2)の説明で使用した低級アルキル基とは、炭素数1から6の直鎖、分岐または環状のアルキル基を示し、具体的な例としては、メチル基、エチル基、プロピル基、ブチル基、2-メチルプロピル基、ヘキシル基などが挙げられる。

【0016】また一般式(1)または(2)において、 R_2 または R_{10} の具体的な例としてはデシル基、ウンデシル基、ドデシル基、トリデシル基、テトラデシル基、ペンタデシル基、ヘキサデシル基、ヘプタデシル基、オ

クタデシル基、ノナデシル基、ドコシル基、トリコシル基、ヘキサコシル基、イコシル基、トリアコシル基、2-メチルデシル基、2-ヘキシルデシル基、6-エチルデシル基、12-メチルテトラデシル基、14-エチルヘキサデシル基、コレステリル基、12-シクロヘキシルドデシル基、1H、1H、2H、2H-ヘプタデカフルオロデシル基、2-ヒドロキシヘキサデシル基、18-ヒドロキシオクタデシル基、16-メトキシヘキサデシル基、14-ブトキシテトラデシル基、12-(ヘキシルチオ)ドデシル基、12-(ヘキシルスルフィニル)ドデシル基、

【0017】12-(ヘキシルスルホニル)ドデシル基、14-(N,N-ジメチルアミノ)テトラデシル基、14-(N-ヘキシルアミノ)テトラデシル基、2-オキシドコシル基、ヘキサデシルオキシカルボニルメチル基、16-(エトキシカルボニル)ヘキサデシル基、16-(ヘキサノイルオキシ)ヘキサデシル基、2-(ドデカノイルオキシ)エチル基、12-(ブタノイルアミノ)ドデシル基、12-(N-ヘキシル(ヘキサノイルアミノ))ドデシル基、16-(N,N-ジブチルアミノカルボニル)ヘキサデシル基、オレイル基、ヘキサデカ-2-エニル基、2-(12-クロロドデシルオキシ)エチル基、10-(イソプロピルオキシ)デシル基、1-エチル-2-(ドデシルオキシ)ブチル基、ファルネシル基、ゲラニル基、ゲラニルゲラニル基などが挙げられる。

【0018】また、一般式(1)および(2)における R_3 、 R_4 、 R_5 、 R_6 、 R_{11} 、 R_{12} の低級アルキルアミノ基の具体的な例としては、メチルアミノ基、エチルアミノ基、プロピルアミノ基、ブチルアミノ基、ヘキシルアミノ基、ジメチルアミノ基、メチルエチルアミノ基、2-メチルプロピルアミノ基などが挙げられ、ヒドロキシ低級アルキルアミノ基の具体的な例としては、ヒドロキシメチルアミノ基、2-ヒドロキシエチルアミノ基、3-ヒドロキシプロピルアミノ基、4-ヒドロキシブチルアミノ基、6-ヒドロキシヘキシルアミノ基、N,N-ビス(2-ヒドロキシエチル)アミノ基、N,N-ビス(4-ヒドロキシブチル)アミノ基、N-(2-ヒドロキシエチル)-N-(4-ヒドロキシブチル)アミノ基などが挙げられ、

【0019】低級アルカノイルアミノ基の具体的な例としては、アセチルアミノ基、プロパノイルアミノ基、ブタノイルアミノ基、ヘキサノイルアミノ基などが挙げられ、低級アルカノイルオキシ基の具体的な例としては、アセトキシル基、プロパノイルオキシ基、ブタノイルオキシ基、ヘキサノイルオキシ基などが挙げられ、低級アルキルスルホニルアミノ基の具体的な例としては、メチルスルホニルアミノ基、エチルスルホニルアミノ基、プロピルスルホニルアミノ基、ブチルスルホニルアミノ基、ヘキシルスルホニルアミノ基などが挙げられ、低級

アルキルスルホニルオキシ基の具体的な例としては、メチルスルホニルオキシ基、エチルスルホニルオキシ基、ブチルスルホニルオキシ基、ヘキシルスルホニルオキシ基などが挙げられ、低級アルコキシ基の具体的な例としては、メトキシ基、エトキシ基、プロポキシ基、ブトキシ基、ヘキシルオキシ基、2-メチルプロポキシ基などが挙げられ、

【0020】ヒドロキシ低級アルコキシ基の具体的な例としては、ヒドロキシメトキシ基、2-ヒドロキシエトキシ基、2-ヒドロキシプロポキシ基、3-ヒドロキシプロポキシ基、2-ヒドロキシブトキシ基、4-ヒドロキシブトキシ基、6-ヒドロキシヘキシルオキシ基などが挙げられ、低級アルキル基の具体的な例としては、メチル基、エチル基、プロピル基、ブチル基、2-メチルプロピル基、ヘキシル基などが挙げられ、低級アルカノイル基の具体的な例としては、アセチル基、プロパノイル基、ブタノイル基、ヘキサノイル基などが挙げられ、ハロゲン原子の具体的な例としては、フッ素、塩素、臭素、ヨウ素が挙げられ、ハロゲン化低級アルキル基の具体的な例としては、クロロメチル基、ブロモメチル基、ヨウ化メチル基、トリフルオロメチル基などが挙げられる。

【0021】上記一般式(1)で示される化合物の薬理学的に許容される塩における、薬理学的に許容されるとは、人体に投与された時において著しい副作用または毒性が出現しないことを、及びその薬理活性を消失させないことを意味する。これらの薬学上許容される塩の具体例として、一般式(1)の化合物がカルボン酸などの酸性を示す官能基を有する場合には、リチウム塩、ナトリウム塩、カリウム塩、マグネシウム塩、カルシウム塩などの金属塩、アンモニア、エチルアミン、ジエチルアミン、トリエチルアミン、トリエタノールアミン、ピペリジン、アニリン、ピリジン等の有機塩基との塩を挙げることができ、一般式(1)の化合物がアミンなどの塩基性を示す官能基を有する場合には、塩酸、臭化水素酸、磷酸、硫酸、メタンスルホン酸、マレイン酸、フマル酸、コハク酸、クエン酸、酒石酸等の無機または有機酸との塩を挙げることができる。

【0022】以下に本発明の一般式(1)で表される化合物の具体例を例示するが、そのプロドラッグ体であるエステルも含まれる。さらに本発明は、これらに限定されるものではない。

- (1) 2- (デシルオキシ) 安息香酸
- (2) 2- (ドデシルオキシ) 安息香酸
- (3) 2- (トリデシルオキシ) 安息香酸
- (4) 2- (テトラデシルオキシ) 安息香酸
- (5) 2- (ペンタデシルオキシ) 安息香酸
- (6) 2- (ヘキサデシルオキシ) 安息香酸
- (7) 2- (ヘプタデシルオキシ) 安息香酸
- (8) 2- (オクタデシルオキシ) 安息香酸

(9) 2- (ノナデシルオキシ) 安息香酸

(10) 2- (ドコシルオキシ) 安息香酸

【0023】(11) 2- (ヘキサコシルオキシ) 安息香酸

(12) 2- (トリアコシルオキシ) 安息香酸

(13) 2- (オレイルオキシ) 安息香酸

(14) 2- (コレステリルオキシ) 安息香酸

(15) 2- (14-エチルヘキサデシルオキシ) 安息香酸

(16) 2- (1H, 1H, 2H, 2H-ヘプタデカフルオロデシルオキシ) 安息香酸

(17) 2- (16-ヒドロキシヘキサデシルオキシ) 安息香酸

(18) 2- (16-メトキシヘキサデシルオキシ) 安息香酸

(19) 2- (3-ヒドロキシヘキサデシルオキシ) 安息香酸

(20) 2- (オクタデシルオキシ) - 3-ニトロ安息香酸

【0024】(21) 2- (ヘキサデシルオキシ) - 3-ニトロ安息香酸

(22) 2- (ヘキサデシルオキシ) - 3-アミノ安息香酸

(23) 2- (ヘキサデシルオキシ) - 3- (メチルアミノ) 安息香酸

(24) 2- (ヘキサデシルオキシ) - 3- (2-ヒドロキシエチルアミノ) 安息香酸

(25) 2- (ヘキサデシルオキシ) - 3- (アセチルアミノ) 安息香酸

(26) 2- (ヘキサデシルオキシ) - 3- (メチルスルホニルアミノ) 安息香酸

(27) 2- (ヘキサデシルオキシ) - 3-ヒドロキシ安息香酸

(28) 2- (ヘキサデシルオキシ) - 3-メトキシ安息香酸

(29) 2- (ヘキサデシルオキシ) - 3- (2-ヒドロキシエトキシ) 安息香酸

(30) 2- (ヘキサデシルオキシ) - 3-アセチル安息香酸

【0025】(31) 2- (ヘキサデシルオキシ) - 6-ヒドロキシ安息香酸

(32) 2- (オクタデシルオキシ) - 6-ヒドロキシ安息香酸

(33) 2- (ヘキサデシルオキシ) - 6-メトキシ安息香酸

(34) 2- (ヘキサデシルオキシ) - 6- (2-ヒドロキシエトキシ) 安息香酸

(35) 2- (ヘキサデシルオキシ) - 6- (4-ヒドロキシブトキシ) 安息香酸

(36) 2- (ヘキサデシルオキシ) - 3-シアノ安息香酸

香酸

(37) 2- (ヘキサデシルオキシ) -3-カルボキシ

安息香酸

(38) 2- (ヘキサデシルオキシ) -6-カルバモイル安息香酸

(39) 2- (ヘキサデシルオキシ) -3-アセトキシ安息香酸

(40) 2- (ヘキサデシルオキシ) -3- (メチルスルホニルオキシ) 安息香酸

【0026】 (41) 2- (ヘキサデシルオキシ) -3, 5-ジクロロ安息香酸

(42) 2- (ヘキサデシルオキシ) -3-ヒドロキシ-6-メチル安息香酸

(43) 2- (ヘキサデシルオキシ) -3-クロロ安息香酸

(44) 2- (ヘキサデシルオキシ) -3-メチル安息香酸

(45) 2- (ヘキサデシルオキシ) -4-ヒドロキシ安息香酸

(46) 2- (ヘキサデシルオキシ) -5-クロロ安息香酸

(47) 2- (ヘキサデシルオキシ) -5-フルオロ安息香酸

(48) 2- (ヘキサデシルオキシ) -5-メチル安息香酸

(49) 2- (ヘキサデシルオキシ) -5-アミノ安息香酸

(50) 2- (ヘキサデシルオキシ) -5-ヒドロキシ安息香酸

【0027】 (51) 2- (ヘキサデシルオキシ) -5-ニトロ安息香酸

(52) 2- (ヘキサデシルオキシ) -5- (クロロメチル) 安息香酸

(53) 2- (ヘキサデシルオキシ) -3- (トリフルオロメチル) 安息香酸

(54) 2- (ヘキサデシルオキシ) -6-ヒドロキシ安息香酸

(55) 2- (オクタデシルオキシ) -6-ニトロ安息香酸

(56) 2- (2- (ドデシルオキシ) エトキシ) 安息香酸

(57) 2- (18-ヒドロキシ (オクタデシルオキシ)) 安息香酸

(58) 2- (12- (ヘキシルチオ) ドデシルオキシ) 安息香酸

(59) 2- (12- (ヘキシルスルホニル) ドデシルオキシ) 安息香酸

(60) 2- (14- (N, N-ジメチルアミノ) テトラデシルオキシ) 安息香酸

【0028】 (61) 2- (2-オキシドコシルオキ

シ) 安息香酸

(62) 2- (ヘキサデシルオキシカルボニルメトキシ) 安息香酸

(63) 2- (16- (エトキシカルボニル) ヘキサデシルオキシ) 安息香酸

(64) 2- (16- (ヘキサノイルオキシ) ヘキサデシルオキシ) 安息香酸

(65) 2- (12- (ブタノイルアミノ) ドデシルオキシ) 安息香酸

(66) 2- (16- (N, N-ジブチルアミノカルボニル) ヘキサデシルオキシ) 安息香酸

(67) 2- (ヘキサデカ-2-イニルオキシ) 安息香酸

(68) 2- (2- (デカノイルオキシ) エトキシエトキシ) 安息香酸

(69) 2- (2- (ヘキサデシルオキシ) エトキシ) -3-ヒドロキシ安息香酸

(70) 2- (2- (ヘキサデシルオキシ) エトキシ) -3-ニトロ安息香酸

【0029】 (71) 2- (ヘキサデシルオキシ) 安息香酸イソブチル

(72) 2- (ヘキサデシルオキシ) 安息香酸エトキシカルボニルメチル

(73) 2- (ヘキサデシルオキシ) 安息香酸ヘキサノイルオキシエチル

(74) 2- (ヘキサデシルオキシ) 安息香酸N, N-ジブチルアミノエチル

(75) 2- (ヘキサデシルオキシ) 安息香酸N, N-ビス (2-ヒドロキシエチル) アミノエチル

(76) 2- (グラニルオキシ) 安息香酸

(77) 2- (ファルネシルオキシ) 安息香酸

(78) 2- (グラニルグラニルオキシ) 安息香酸

(79) 2- (10-フェニルデシルオキシ) 安息香酸

(80) 2- (ヘキサデシルチオ) 安息香酸

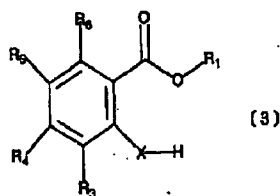
(81) 2- (オクタデシルチオ) 安息香酸

またはこれらの塩。これらの化合物は、1種または2種以上混合して用いてもよい。

【0030】なお、従来の技術の項で説明したように、一般式(1)で表される化合物の中には公知化合物が含まれているが、PLA₂阻害作用を示すことは全く知られていない。また、一般式(2)で示される請求項2および請求項3の化合物群は、新規な化合物である。一般式(1)および(2)の化合物は、例えば以下の一般的方法により製造される。一般式(3)【化5】

【0031】

【化5】



(式中、X、R₁、R₃、R₄、R₅、R₆は一般式(1)の場合と同じ。)で表される化合物に、一般式(4)

[化6]

【0032】

[化6] R₂-OH (4)

(式中、R₂は一般式(1)の場合と同じ。)で表される化合物を一般式(3)で表される化合物に対して0.2~10.0モル量、より好ましくは0.5~2.0モル量、さらに好ましくは0.8~1.5モル量加え、さらにトリフェニルホスフィンを用いて一般式(3)で表される化合物に対して0.8~2.0モル量、より好ましくは1.0~1.2モル量加えて適当な溶媒に溶解あるいは懸濁し、アゾジカルボン酸ジエチルを用いて一般式(3)で表される化合物に対して0.8~2.0モル量、より好ましくは1.0~1.2モル量を滴下して加え反応させることにより、一般式(1)で表される化合物を得ることができる。

【0033】この反応は-30℃から当該反応混合物の還流温度以下の温度で行われ、好ましくは-5~50℃、さらに好ましくは20~40℃の範囲から反応温度が選ばれる。この反応に用いる適当な溶媒としては、この反応に対して不活性な溶媒ならば制限なく使用でき、例えばテトラヒドロフラン、ジメチルホルムアミド、クロロホルム、ジクロロメタン、酢酸エチル、ジオキサン、ベンゼン、ジメチルスルホキシド等を使用することができる。

【0034】また、一般式(3)及び(4)で表される化合物に主反応部位以外の活性官能基が存在する場合は、適当な保護基を用いて反応した後に脱保護することが好ましい。目的物の精製はカラムクロマトグラフィー、再結晶、蒸留などの一般的方法により行うことができる。一般式(2)の化合物も同様に製造される。

【0035】さらに、プロドラッグとして、安息香酸のカルボキシル基のエステル体を合成する際には、相当するカルボン酸を塩化チオニル等で酸塩化物に導いた後に、相当するアルコール(例えば、N、N-ジメチルアミノエタノール等)と反応させるか、相当するカルボン酸とアルコールをジシクロヘキシルカルボジイミド(以下、DCCと略記)、カルボジイミダゾール(以下、CDIと略記)、アゾジカルボン酸ジエチル等の縮合剤存在下反応させることにより容易に目的とするエステル体を得られる。この際、反応物のモル比は任意の比で使用可能であるが、好ましくは、0.8~1.2当量である。溶媒も特に限定されないが、THF、エチルエーテ

ル、ジオキサン、トルエン、ピリジン、トリエチルアミン、クロロホルム、塩化メチレンまたは酢酸エチル等の非プロトン性有機溶媒が使用される。反応温度としては、0℃から使用する溶媒の沸点まで許容されるが、好ましくは室温付近である。

【0036】さらに、一般式(1)および(2)で表される化合物は、適当な酸または塩基を加えることにより、薬理的に許容される塩に導くことができる。

【0037】本発明の抗炎症剤を炎症性疾患治療薬として用いる場合、その投与量、剤形は、有効成分として用いる一般式(1)および(2)で表される化合物の物性、投与対象の症状、年齢、性別により異なるが、例えば成人1日あたり10~5,000mg、好ましくは10~1,000mgをそのままあるいは治療的に不活性な賦形剤を添加した医薬用組成物として経口的に粉剤、顆粒剤、錠剤、カプセル剤等の剤形で、または非経口的に座剤、注射剤、輸液用等張液、吸入剤あるいは貼付剤等の剤形で投与することができる。

【0038】製剤中における有効成分の含有量は特に制限はないが通常は1~90%である。なお、本発明のPLA₂阻害剤の毒性は、炎症性疾患治療薬として用いるには問題がないレベルである。

【0039】

【実施例】以下に本発明の実施例として、化合物の製造例、医薬製剤の製造例および薬理試験例を挙げて詳細に説明する。なお、本発明は以下の実施例のみに限定されるものではない。

(化合物の製造例)

実施例1 2-(デシルオキシ)安息香酸メチル

サリチル酸メチル1.00g、デカノール1.09g、トリフェニルホスフィン1.81gをTHF10mlに溶解し、アゾジカルボン酸ジエチル1.30gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して粗製の2-(デシルオキシ)安息香酸メチルを得て、これをシリカゲルカラムクロマトグラフィー(展開溶媒：酢酸エチル/n-ヘキサン=1/5)で精製し、2-(デシルオキシ)安息香酸メチル1.78gを得た。NMR(CDC1₃) δ ppm: 7.77(1H, dd)、7.42(1H, dt)、6.89~7.02(2H, m)、4.00(2H, t)、3.88(3H, s)、1.76~1.89(2H, m)、1.27~1.60(14H, m)、0.87(3H, t)。性状：油状物。

【0040】実施例2 2-(デシルオキシ)安息香酸
実施例1で得られた化合物1.75gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて50℃で3時間攪拌し加水分解した。反応液を塩酸で中和してから減圧濃縮し、析出物を水洗後、濾過して集めた。これを少量のメタノールから再結晶

し、2- (デシルオキシ) 安息香酸 1.54 g を得た。
NMR (CDCl₃) δ ppm; 8.20 (1H, d), 7.54 (1H, dt), 7.13 (1H, dt), 7.04 (1H, dd), 4.25 (2H, t), 1.87~1.97 (2H, m), 1.01~1.79 (14H, m), 0.88 (3H, t)。性状: 油状物。

【0041】実施例1及び2に準じて、以下の実施例3から17の化合物を合成した。

実施例3 2- (トリデシルオキシ) 安息香酸メチル
NMR (CDCl₃) δ ppm; 7.80 (1H, d), 7.43 (1H, dt), 6.91~6.98 (2H, m), 4.03 (2H, t), 3.89 (3H, s), 1.78~1.88 (2H, m), 1.23~1.51 (20H, m), 0.88 (3H, t)。性状: 油状物。

【0042】実施例4 2- (トリデシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 8.19 (1H, d), 7.54 (1H, dt), 7.07 (1H, dt), 6.89 (1H, dd), 4.23 (2H, t), 1.90~1.95 (2H, m), 0.91~1.88 (20H, m), 0.87 (3H, t)。融点: 43~44℃。

【0043】実施例5 2- (ペンタデシルオキシ) 安息香酸メチル

NMR (CDCl₃) δ ppm; 7.79 (1H, d), 7.46 (1H, dt), 6.91~7.00 (2H, m), 4.02 (2H, t), 3.89 (3H, s), 1.77~1.88 (2H, m), 1.26~1.51 (24H, m), 0.88 (3H, t)。融点: 33~34℃。

【0044】実施例6 2- (ペンタデシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 8.20 (1H, d), 7.56 (1H, dt), 7.13 (1H, t), 7.05 (1H, d), 4.26 (2H, t), 1.87~1.97 (2H, m), 1.43~1.49 (2H, m), 1.23~1.33 (22H, m), 0.88 (3H, t)。融点: 54~56℃。

【0045】実施例7 2- (ヘキサデシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 0.88 (t, 3H), 1.26~1.68 (m, 22H), 1.87~2.01 (m, 2H), 4.25 (t, 2H), 7.04 (dd, 1H), 7.14 (dt, 1H), 7.55 (dt, 1H), 8.20 (dd, 1H)。融点: 56~58℃。

【0046】実施例8 2- (ヘプタデシルオキシ) 安息香酸メチル

NMR (CDCl₃) δ ppm; 7.77 (1H, d), 7.40~7.46 (1H, m), 6.85~6.98 (2H, m), 4.03 (2H, t), 3.89 (3H, s), 1.80~1.88 (2H, m), 1.26~1.50 (28H, m), 0.88 (3H, t)。融点: 39~40℃。

【0047】実施例9 2- (ヘプタデシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 8.20 (1H, d), 7.55 (1H, dt), 7.14 (1H, t), 7.04 (1H, d), 4.25 (2H, t), 1.87~1.97 (2H, m), 1.42~1.52 (2H, m), 1.22~1.36 (26H, m), 0.88 (3H, t, J=7.3)。融点: 61~64℃。

【0048】実施例10 2- (ノナデシルオキシ) 安息香酸メチル

NMR (CDCl₃) δ ppm; 7.76~7.80 (1H, m), 7.37~7.47 (1H, m), 6.93~7.00 (2H, m), 4.03 (2H, t), 3.89 (3H, s), 1.80~1.88 (2H, m), 1.26~1.49 (32H, m), 0.88 (3H, t)。融点: 44~46℃。

【0049】実施例11 2- (ノナデシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 8.20 (1H, d), 7.55 (1H, dt), 7.14 (1H, t), 7.05 (1H, d), 4.25 (2H, t), 1.87~1.97 (2H, m), 1.46~1.58 (2H, m), 1.22~1.44 (30H, m), 0.88 (3H, t)。融点: 67~68℃。

【0050】実施例12 2- (ドコシルオキシ) 安息香酸メチル

NMR (CDCl₃) δ ppm; 7.58~7.93 (1H, m), 7.39~7.46 (1H, m), 6.93~6.98 (2H, m), 4.02 (2H, t), 3.88 (3H, s), 1.77~1.87 (2H, m), 1.25~1.53 (38H, m), 0.88 (3H, t)。融点: 64~65℃。

【0051】実施例13 2- (ドコシルオキシ) 安息香酸

NMR (CDCl₃) δ ppm; 8.20 (1H, d), 7.55 (1H, dt), 7.14 (1H, t), 7.05 (1H, d), 4.25 (2H, t), 1.87~1.97 (2H, m), 1.46~1.58 (2H, m), 1.22~1.44 (36H, m), 0.88 (3H, m)。融点: 74~75℃。

【0052】実施例14 2- (オクタデシルオキシ) -3-ニトロ安息香酸メチル

NMR (CDCl₃) δ ppm; 8.00 (1H, d

d)、7.88 (1H, dd)、7.14~7.28 (1H, m)、4.07 (2H, t)、3.95 (3H, s)、1.75~1.85 (2H, m)、1.39~1.45 (2H, m)、1.26~1.39 (28H, m)、0.88 (3H, t)。融点:46-48℃。

【0053】実施例15 2-(オクタデシルオキシ)-3-ニトロ安息香酸

NMR (CDCl₃) δ ppm; 8.33 (1H, d)、8.05 (1H, dt)、7.38 (1H, t)、4.17 (2H, t)、1.83~1.93 (2H, m)、1.41~1.44 (2H, m)、1.26~1.38 (28H, m)、0.88 (3H, t)。融点:66-67℃。

【0054】実施例16 2-(ドコシルオキシ)-3-ニトロ安息香酸メチル

NMR (CDCl₃) δ ppm; 8.00 (1H, d)、7.88 (1H, dd)、7.14~7.28 (1H, m)、4.07 (2H, t, J=6.5)、3.95 (3H, s)、1.75~1.85 (2H, m)、1.39~1.45 (2H, m)、1.26~1.39 (36H, m)、0.88 (3H, t, J=7.3)。融点:58-60℃。

【0055】実施例17 2-(ドコシルオキシ)-3-ニトロ安息香酸

NMR (CDCl₃) δ ppm; 8.32 (1H, d)、8.04 (1H, dt)、7.37 (1H, t)、4.17 (2H, t)、1.82~1.93 (2H, m)、1.40~1.44 (2H, m)、1.25~1.39 (36H, m)、0.88 (3H, t)。融点:73-75℃。

【0056】実施例18 2-(ヘキサデシルオキシ)-3-ヒドロキシ安息香酸メチル

2, 3-ジヒドロキシ安息香酸メチル1.00gをピリジン1.5gに溶解し、これに無水酢酸0.67gを滴下して室温で1夜攪拌した。反応液を氷水にあげて反応を停止し、析出した結晶を濾別した。メタノールから再結晶し、3-アセトキシ-2-ヒドロキシ安息香酸メチル0.99gを得た。得られた3-アセトキシ-2-ヒドロキシ安息香酸メチル0.99g、ヘキサデカノール1.14g、トリフェニルホスフィン1.23gをTHF10mlに溶解し、アゾジカルボン酸ジエチル0.98gのTHF3ml溶液を滴下し、室温で1時間攪拌した。

【0057】減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して粗製の2-(ヘキサデシルオキシ)-3-アセトキシ安息香酸メチルを得て、これをシリカゲルカラムクロマトグラフィー(展開溶媒:酢酸エチル/n-ヘキサン=1/5)で精製し、2-(ヘキサデシルオキ

シ)-3-アセトキシ安息香酸メチルを1.74g得た。これをメタノール10mlに溶解し、さらに28%ナトリウムメトキシドのメタノール溶液8mlを加えて、室温で1時間攪拌した。これに希塩酸を加えて酸性にした後、大量の水にあげて酢酸エチルで抽出し、2-(ヘキサデシルオキシ)-3-ヒドロキシ安息香酸メチルを1.57g得た。

NMR (CDCl₃) δ ppm; 7.38 (1H, d)、7.14 (1H, dd)、7.03 (1H, t)、5.92 (1H, s)、3.98 (2H, t)、3.91 (3H, s)、1.76~1.87 (2H, m)、1.26~1.45 (26H, m)、0.88 (3H, t)。性状:油状物。

【0058】実施例19 2-(ヘキサデシルオキシ)-3-ヒドロキシ安息香酸

実施例18で得られた化合物1.55gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて60℃で4時間攪拌し加水分解した。反応液に濃塩酸を加えて酸性とし、析出物を濾過、水洗、乾燥して2-(ヘキサデシルオキシ)-3-ヒドロキシ安息香酸1.37gを得た。

NMR (CDCl₃) δ ppm; 7.63 (1H, d)、7.13~7.17 (2H, m)、4.11 (2H, t)、1.81~1.92 (2H, m)、1.25~1.46 (26H, m)、0.88 (3H, t)。融点:92-98℃。

【0059】実施例20 2-(ヘキサデシルオキシ)-3-(メチルスルホニルアミノ)安息香酸

3-ニトロサリチル酸メチル1.00g、ヘキサデカノール1.23g、トリフェニルホスフィン1.33gをTHF10mlに溶解し、アゾジカルボン酸ジエチル0.88gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して残渣にメタノール20mlを加えて攪拌し、氷冷後に濾過し2-(ヘキサデシルオキシ)-3-ニトロ安息香酸メチルを1.97g得た。この化合物を酢酸エチルに溶解し、10%Pd/C 0.06gを加え、常圧で水素添加した。1.6時間後、触媒を濾過で除き、減圧濃縮して、2-(ヘキサデシルオキシ)-3-アミノ安息香酸メチル1.88gを得た。

【0060】これにトリエチルアミン0.66gを加え、これにクロロホルム25mlを加えて溶解し、氷冷した。メタンサルホン酸クロリド0.66gをクロロホルム10mlに溶解して滴下した後、30分間攪拌した。反応液を水洗後、減圧濃縮して2-(ヘキサデシルオキシ)-3-(メチルスルホニルアミノ)安息香酸メチルを得た。これをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて50℃で3時間攪拌し加水分解した。反応液に濃塩酸を加えて

酸性とし、析出物を濾過、水洗、乾燥して2-(ヘキサデシルオキシ)-3-(メチルスルホニルアミノ)安息香酸2.18gを得た。

NMR (CDCl₃) δ ppm; 7.80 (1H, d), 7.78 (1H, t), 7.23 (1H, d), 4.03 (2H, t), 3.08 (3H, s), 1.80~1.90 (2H, m), 1.20~1.60 (26H, m), 0.88 (3H, t)。融点: 92-94℃。

【0061】実施例21 2-(ヘキサデシルオキシ)-3-メトキシ安息香酸メチル
2-ヒドロキシ-3-メトキシ安息香酸メチル1.00g、ヘキサデカノール1.33g、トリフェニルホスフィン1.44gをTHF10mlに溶解し、アゾジカルボン酸ジエチル1.20gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して残渣にメタノール20mlを加えて攪拌し、氷冷後に濾過し、2-(ヘキサデシルオキシ)-3-メトキシ安息香酸メチルを1.76gを得た。

NMR (CDCl₃) δ ppm; 7.32 (1H, q), 7.01~7.23 (2H, m), 4.01 (2H, t), 3.89 (3H, s), 3.86 (3H, s), 1.73~1.84 (2H, m), 1.26~1.56 (26H, m), 0.88 (3H, t)。融点: 32-33℃。

【0062】実施例22 2-(ヘキサデシルオキシ)-3-メトキシ安息香酸
実施例20で得られた化合物1.70gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて60℃で5時間攪拌して加水分解した。反応液に濃塩酸を加えて酸性とし、析出物を濾過、水洗、乾燥して2-(ヘキサデシルオキシ)-3-メトキシ安息香酸1.69gを得た。

NMR (CDCl₃) δ ppm; 11.59 (1H, b s), 7.74 (1H, q), 7.13~7.20 (2H, m), 4.26 (2H, t), 3.91 (3H, s), 1.78~1.91 (2H, m), 1.06~1.54 (26H, m), 0.88 (3H, t)。融点: 62-63℃。

【0063】実施例23 2-(ヘキサデシルオキシ)-3-(2-ヒドロキシエトキシ)安息香酸
2-(ヘキサデシルオキシ)-3-ヒドロキシ安息香酸メチル1.18g、モノアセチルエチレングリコール0.31g、トリフェニルホスフィン0.79gをTHF10mlに溶解し、アゾジカルボン酸ジエチル0.63gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、ついでシリカゲルカラムクロマトグラフィー(展開溶媒: n-ヘキサン/酢酸エチル=15/

1→10/1)により処理し、3-(2-アセトキシエトキシ)-2-(ヘキサデシルオキシ)安息香酸メチル1.41gを得た。これをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて60℃で5時間攪拌して加水分解した。反応液に濃塩酸を加えて酸性とし、析出物を濾過、水洗、乾燥して、2-(ヘキサデシルオキシ)-3-(2-ヒドロキシエトキシ)安息香酸0.64gを得た。

NMR (CDCl₃) δ ppm; 7.77 (1H, m), 7.19 (2H, m), 4.29 (2H, t), 4.18 (2H, t), 4.03 (2H, t), 1.80~1.91 (2H, m), 1.26~1.46 (26H, m), 0.88 (3H, t)。融点: 71-74℃。

【0064】実施例24 2-(ヘキサデシルオキシ)-6-ヒドロキシ安息香酸メチル
2,6-ジヒドロキシ安息香酸メチル1.00gとヘキサデシルアルコール1.44g、トリフェニルホスフィン1.56gをTHF10mlに溶解し、アゾジカルボン酸ジエチル1.20gのTHF3ml溶液を滴下した。室温で1時間攪拌後、減圧濃縮し、シリカゲルカラムクロマトグラフィー(展開溶媒: 酢酸エチル/n-ヘキサン=1/5)で精製し、2-(ヘキサデシルオキシ)-6-ヒドロキシ安息香酸メチル1.53gを得た。

NMR (CDCl₃) δ ppm; 7.30 (1H, d), 6.57 (1H, d), 6.38 (1H, d), 3.98 (2H, t), 3.93 (3H, s), 1.78~1.83 (2H, m), 1.42~1.60 (2H, m), 1.20~1.40 (24H, m), 0.88 (3H, t)。融点: 52-53℃。

【0065】実施例25 2-(ヘキサデシルオキシ)-6-ヒドロキシ安息香酸
実施例24で得られた化合物1.5gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて70℃で4時間攪拌して加水分解した。反応液を濃塩酸を加えて酸性とし、析出物を濾過、水洗、乾燥して、2-(ヘキサデシルオキシ)-6-ヒドロキシ安息香酸0.89gを得た。

NMR (CDCl₃) δ ppm; 7.39 (1H, t), 6.71 (1H, d), 6.47 (1H, d), 4.23 (2H, t), 1.88~1.91 (2H, m), 1.40~1.60 (2H, m), 1.20~1.50 (24H, m), 0.88 (3H, t)。融点: 92-95℃。

【0066】実施例26 2-(オクタデシルオキシ)-6-ヒドロキシ安息香酸
2,6-ジヒドロキシ安息香酸メチル1.00gとオクタデシルアルコール1.61g、トリフェニルホスフィン1.87gをTHF10mlに溶解し、アゾジカルボ

ン酸ジエチル1.24gのTHF3ml溶液を滴下した。室温で1時間攪拌後、減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して残渣にメタノール20mlを加えて攪拌し、氷冷後に濾過し、粗製の2-(オクタデシルオキシ)-6-ヒドロキシ安息香酸メチルを得た。これをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて70℃で5時間加熱攪拌して加水分解した。反応液を濃塩酸を加えて酸性とし、析出物を濾過、水洗、乾燥しシリカゲルカラムクロマトグラフィー(展開溶媒:クロロホルム/n-ヘキサン=2/5)で精製し、2-(オクタデシルオキシ)-6-ヒドロキシ安息香酸0.59gを得た

NMR (CDCl₃) δ ppm: 7.37 (1H, t), 6.71 (1H, d), 6.47 (1H, d), 4.23 (2H, t), 1.85~1.97 (2H, m), 1.20~1.70 (30H, m), 0.88 (3H, t)。融点: 59~61℃。

【0067】実施例27 2-(3-ヒドロキシペンタデシルオキシ)安息香酸

サリチル酸メチル1.00g、3-ヒドロキシペンタデカ-1-オール1.61g、トリフェニルホスフィン1.81gをTHF10mlに溶解し、アゾジカルボン酸ジエチル1.30gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングして不溶物を濾過して除き、濾液を濃縮して粗製の2-(3-ヒドロキシペンタデシルオキシ)安息香酸メチルを得て、これをシリカゲルカラムクロマトグラフィー(展開溶媒:酢酸エチル/n-ヘキサン=1/5)で精製し、2-(3-ヒドロキシペンタデシルオキシ)安息香酸メチル1.07gを得た。このエステル化合物1.00gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて50℃で3時間攪拌し加水分解した。

【0068】反応液を塩酸で中和してから減圧濃縮し、析出物を水洗後、濾過して集めた。これを少量のメタノールから再結晶し、2-(3-ヒドロキシペンタデシルオキシ)安息香酸0.92gを得た。

NMR (CDCl₃) δ ppm: 8.18 (1H, d), 7.55 (1H, dt), 7.11 (1H, t), 7.05 (1H, d), 4.43~4.47 (1H, t), 4.30~4.36 (1H, m), 3.86~3.95 (1H, m), 2.00~2.11 (1H, m), 1.52~1.62 (2H, m), 1.26~1.42 (22H, m), 0.88 (3H, t)。融点: 80~82℃。

【0069】実施例28 2-(2-(ドデシルオキシ)エトキシ)安息香酸

サリチル酸メチル1.00g、2-(ドデシルオキシ)エタノール1.51g、トリフェニルホスフィン1.8

1gをTHF10mlに溶解し、アゾジカルボン酸ジエチル1.30gのTHF3ml溶液を滴下し、室温で1時間攪拌した。減圧濃縮し、残渣にn-ヘキサン50mlを加えてスラッジングし、不溶物を濾過して除き、濾液を濃縮して粗製の2-(2-(ドデシルオキシ)エトキシ)安息香酸メチルを得て、これをシリカゲルカラムクロマトグラフィー(展開溶媒:酢酸エチル/n-ヘキサン=1/5)で精製し、2-(2-(ドデシルオキシ)エトキシ)安息香酸メチル0.79gを得た。

【0070】このエステル化合物0.75gをメタノール30mlに溶解し、さらに10%水酸化ナトリウム水溶液5mlを加えて50℃で3時間攪拌し加水分解した。反応液を塩酸で中和してから減圧濃縮し、析出物を水洗後、濾過して集めた。これを少量のメタノールから再結晶し、2-(2-(ドデシルオキシ)エトキシ)安息香酸0.69gを得た。

NMR (CDCl₃) δ ppm: 8.18 (1H, d), 7.55 (1H, dt), 7.15 (1H, t), 7.05 (1H, d), 4.33~4.39 (2H, m), 3.82~3.85 (2H, m), 3.53 (2H, m), 1.59~1.64 (4H, m), 1.25~1.29 (16H, m), 0.88 (3H, t)。融点: 44~46℃。

【0071】実施例29 2-(ヘキサデシルチオ)安息香酸

チオサリチル酸メチル1.68gのTHF溶液20mlにトリフェニルホスフィン5.25g(1.0当量)、1-ヘキサデカノール7.27g(3.0当量)を溶解させ、ここに室温でアゾジカルボン酸ジエチル3.48g(2.0当量)のTHF12ml溶液をゆっくり滴下した。滴下終了後室温で攪拌、一晚放置した。この反応液をn-ヘキサンでスラッジングして不溶物を濾過して除き、濾液を濃縮、濃縮後シリカゲルカラムクロマトグラフィー(展開溶媒: n-ヘキサン/酢酸エチル=10/1)で精製し、目的物4.67g(収率76%)を得た。

【0072】このエステル体4.67gをメタノール40mlとジオキサン60mlの混合液に溶解し、これに2Nの水酸化ナトリウム水溶液5.7mlを加えて攪拌、一晚放置した。これに1N塩酸を加えて中和してから大量の水で希釈し、酢酸エチルで抽出し、濃縮後カラム精製(展開溶媒: n-ヘキサン/酢酸エチル=5/1→クロロホルム)を行い、目的物0.50g(収率17%)を得た。

NMR (CDCl₃) δ ppm: 0.88 (t, 3H), 1.22~1.35 (m, 26H), 1.40~1.55 (m, 2H), 1.68~1.78 (m, 2H), 2.93 (t, 2H), 7.21 (t, 1H), 7.37 (d, 1H), 7.49 (dt, 1H), 8.14 (dd, 1H)

【0073】実施例30 2-（ペンタデシルチオ）安息香酸

実施例2と同様の操作で、相当するアコールに1-ペンタデカノールを使用して、2-（ペンタデシルチオ）安息香酸を合成した。

NMR (CDCl₃) δ ppm; 0.88 (t, 3H)、1.25-1.35 (m, 24H)、1.40-1.50 (m, 2H)、1.66-1.78 (m, 2H)、2.93 (t, 2H)、7.23 (t, 1H)、7.38 (d, 1H)、7.49 (dt, 1H)、8.14 (dd, 1H)。

【0074】実施例31 2-（1H、1H、2H、2H、ヘプタデカフルオロデカオキシ）安息香酸

実施例27と同様の操作で、相当するアルコールに1H、1H、2H、2H、ヘプタデカフルオロデカノールを使用して、2-（1H、1H、2H、2H、ヘプタデカフルオロデカオキシ）安息香酸を合成した。

NMR (CDCl₃) δ ppm; 2.68-2.86 (m, 2H)、4.56 (t, 2H)、7.06 (d, 1H)、7.19 (t, 1H)、7.60 (dt, 1H)、8.20 (dd, 1H)。融点: 79-81.5℃。

【0075】実施例32 2-オレイルオキシ安息香酸メチル

サリチル酸メチル 1.00g の THF溶液 10ml にトリフェニルホスフィン 1.81g (1.05当量)、オレイルアルコール（純度60%）3.00g (1.05当量)を溶解させ、ここに室温でアゾジカルボン酸ジエチル 1.38g (1.21当量)の THF溶液 3mlをゆっくり滴下した。滴下終了後室温で攪拌、一晚放置した。この反応液をn-ヘキサンでスラッシングして不溶物を濾過して除き、濾液を濃縮後シリカゲルカラムクロマトグラフィー（展開溶媒: n-ヘキサン/酢酸エチル=50/1）で精製し、表題化合物 1.67g (収率63%)を得た。

NMR (CDCl₃) δ ppm; 0.88 (t, 3H)、1.2-2.1 (m, 31H)、3.88 (s, 3H)、4.02 (t, 2H)、5.34 (t, 2H)、6.9-7.0 (m, 2H)、7.4-7.5 (t, 1H)、7.75-7.80 (dd, 1H)。性状: 油状物。

【0076】実施例33 2-（フィトキシ）安息香酸サリチル酸メチル 1.00g の THF溶液 13ml にトリフェニルホスフィン 1.81g (1.05当量)、フィトール 2.06g (1.06当量)を溶解させ、ここに室温でアゾジカルボン酸ジエチル 1.38g (1.21当量)の THF溶液 5mlをゆっくり滴下した。滴下終了後室温で攪拌、一晚放置した。この反応液をn-ヘキサンでスラッシングし、濃縮後シリカゲルカラムクロマトグラフィー（展開溶媒: n-ヘキサン/酢

酸エチル=15/1）で精製し、さらに、酢酸エチル 50mlに溶解させ、10%水酸化ナトリウム水溶液および飽和食塩水で洗浄、無水硫酸ナトリウムで乾燥した。濃縮乾固、減圧乾燥を行い、エステル体の淡黄色液体 2.05g (収率72%)を得た。

【0077】このエステル体 1.50gのメタノール溶液 10mlに10%水酸化ナトリウム水溶液 10mlを加え、油温 70℃で3時間加熱攪拌した。室温まで放冷後、1.2N塩酸で中和してから大量の水で希釈し、酢酸エチルで抽出した。無水硫酸ナトリウムで乾燥後、濃縮乾固および減圧乾燥し、目的物の黄色液体 1.45g (収率72%)を得た。

NMR (CDCl₃) δ ppm; 0.86 (t, 12H)、1.00-1.57 (m, 19H)、1.77 (s, 3H)、2.07 (t, 2H)、4.79 (d, 2H)、5.53 (t, 1H)、7.06 (d, 1H)、7.13 (t, 1H)、7.55 (dt, 1H)、8.20 (dd, 1H)。性状: 油状物。

【0078】以下実施例33と同様の反応を行い、目的化合物を得た。

実施例34 2-（ファルネシルオキシ）安息香酸

NMR (CDCl₃) δ ppm; 1.60-2.20 (m, 20H)、4.78 (t, 2H)、5.08-5.11 (br, 2H)、5.53 (t, 1H)、7.05 (dd, 1H)、7.13 (t, 1H)、7.55 (dt, 1H)、8.20 (dd, 1H)。性状: 油状物。

【0079】実施例35 2-（10-フェニル-n-デカノキシ）安息香酸

NMR (CDCl₃) δ ppm; 1.22-1.64 (m, 14H)、1.86-1.97 (m, 2H)、2.60 (t, 2H)、4.25 (t, 2H)、7.04 (d, 1H)、7.10-7.30 (m, 6H)、7.55 (dt, 1H)、8.20 (dd, 1H)。性状: 油状物。

【0080】実施例36 2-（15-カルボキシル-ペンタデカノキシ）安息香酸

NMR (DMSO) δ ppm; 1.23 (m, 24H)、1.6-1.75 (m, 2H)、2.18 (t, 2H)、4.01 (t, 2H)、6.97 (t, 1H)、7.09 (d, 1H)、7.46 (t, 1H)、7.59 (dd, 1H)。融点: 84-86.5℃。

【0081】実施例37 2-（12-（p-カルボキシルフェノキシ）ドデシルオキシ）安息香酸

NMR (DMSO) δ ppm; 1.20-1.50 (m, 16H)、1.65-1.80 (m, 4H)、3.95-4.05 (m, 4H)、6.90-7.05 (m, 3H)、7.09 (d, 1H)、7.43 (dt, 1H)、7.60 (dd, 1H)、7.87 (d, 2H)。融点: 146-147.5℃。

【0082】実施例38 2-(12-(α -カルボキシルフェノキシ)ドデシルオキシ)安息香酸

NMR (DMSO) δ ppm; 1.20-1.50 (m, 16H)、1.60-1.80 (m, 4H)、4.00 (t, 4H)、6.96 (t, 2H)、7.09 (d, 2H)、7.45 (dt, 1H)、7.60 (dd, 1H)。融点: 136.5-138.5°C。

【0083】実施例39 N,Nジメチルアミノエチル 2-(1-ヘキサデシルオキシ)安息香酸エステル塩酸塩

実施例7で得られた2-(1-ヘキサデシルオキシ)安息香酸0.5g (1.38mmol)をチオニクロライド1.6g (13.8mmol)に溶解し、室温で攪拌し、一夜放置した。チオニクロライドを留去し、2-(1-ヘキサデシルオキシ)安息香酸クロライドを結晶として得た。これをこのまま次の反応に使用した。N,Nジメチルアミノエタノール0.13g (1.51mmol)をピリジン5mlに溶解し、窒素気流下、水冷して、上記クロライドをメチレンクロライド5mlに溶解し、10分で滴下した。徐々に室温に戻し、3時間攪拌した。

【0084】ピリジンを留去し、エチルエーテル/NaHCO₃水溶液で中和、抽出し、エチルエーテル層を飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥、濃縮することで粗製のプロドラッグ体0.57gを得た。これをカラムクロマトグラフィー(展開溶媒: CHCl₃→CHCl₃/MeOH=50/1→20/1)により処理し、精製物0.5gを得た。(収率84.7%)
NMR (DMSO) δ ppm; 0.85 (t, 3H)、1.23-1.43 (m, 26H)、1.65-1.72 (m, 2H)、2.19 (s, 6H)、2.56 (t, 2H)、4.01 (t, 2H)、4.27 (t, 2H)、6.99 (t, 1H)、7.11 (d, 1H)、7.49 (dt, 1H)、7.60 (dd, 1H)。性状: 油状物。

【0085】上記エステル体14.00gに4N-ジオキサン塩酸8.9mlを加えた。氷水で冷却しながら振り動かし、析出した固体を濾別、酢酸エチル洗浄、減圧乾燥して、目的物の塩酸塩を12.32g (収率81.1%)得た。

NMR (DMSO) δ ppm; 0.85 (t, 3H)、1.24-1.42 (m, 26H)、1.66-1.76 (m, 2H)、2.83 (s, 6H)、3.47 (t, 2H)、4.03 (t, 2H)、4.55 (t, 2H)、7.01 (t, 1H)、7.15 (d, 1H)、7.54 (dt, 1H)、7.81 (dd, 1H)。融点: 84-88°C。

【0086】実施例40 N,Nジメチルアミノ 2-(フィトキシ)安息香酸エステル塩酸塩

実施例33で得られた2-(フィトキシ)安息香酸0.

5gのTHF溶液5mlにジエチルアザカルボン酸ジエチル0.22g (1.05当量)のTHF溶液1mlを添加し、ここにN,Nジメチルアミノエタノール0.12g (1.12当量)のTHF溶液4mlを約5分かけて滴下後、室温で30分攪拌した。反応液を濃縮し、酢酸エチルを少量加え、n-ヘキサンでスラッシングして不溶物を濾過して除き、濾液を濃縮後、シリカゲルカラムクロマトグラフィー(展開溶媒: CHCl₃/MeOH=100/0~100/1)を行い、プロドラッグ体の黄色液体0.27g (収率46.6%)を得た。

【0087】この全量に4N-ジオキサン塩酸0.17mlを加え、室温で約10分振り動かし、濃縮乾固、減圧乾燥を行い、目的物の黄色液体0.29g (収率: ほぼ定量的)を得た。

NMR (DMSO) δ ppm; 0.85 (t, 12H)、1.05-1.55 (m, 19H)、1.69 (s, 3H)、2.00 (t, 2H)、3.33 (s, 6H)、3.47 (t, 2H)、4.55 (t, 2H)、4.64 (d, 2H)、5.38 (t, 1H)、7.02 (t, 1H)、7.15 (d, 1H)、7.54 (dt, 1H)、7.79 (dd, 1H)。性状: 油状物。

【0088】(医薬剤の製造例)

実施例41 2-(ペンタデシルオキシ)安息香酸ナトリウムの注射剤の製造

2-(ペンタデシルオキシ)安息香酸ナトリウム20mgおよび塩化ナトリウム0.85gをとり、これを適量の注射用蒸留水を加えて溶解し全量を100mlとし、メンブレンフィルターで除菌濾過して注射剤とした。

【0089】実施例42 2-(ペンタデシルオキシ)安息香酸の錠剤の製造

2-(ペンタデシルオキシ)安息香酸1g、乳糖123gおよびトウモロコシデンプン20gをよく混合し、これをヒドロキシプロピルセルロース5gを水100mlに溶解した液で混合造粒し、50°Cで4時間乾燥した。これにステアリン酸マグネシウム1gを加えてよく混合し、打錠機を用い、1錠あたり150mgの重量で製錠した。

【0090】(薬理試験例)

実施例43 PLA₂阻害作用

一般式(1)で表される代表的化合物のI型PLA₂に対する阻害作用は、カツマタらの方法[Analytical Biochemistry, 154, 676(1986)]に基づいて測定した。測定方法は以下の通りである。ネジ蓋付試験管に終濃度が100mM tris-塩酸緩衝液(pH=8.0)、0.01mg/ml ウシ血清アルブミン、2mM 塩化カルシウムとなるように調製した溶液に、検体を濃度が10、100、500μMとなるように精製水またはジメチルスルホキシド10μlに溶解して添加した。これにブタ膵臓由来のPLA₂(Boehringer

Mannheim社製)を試験管あたり50mUを1mg/mlのウシ血清アルブミンを含む10ml tris-塩酸緩衝液(pH=8.0)に溶解して添加し、37℃で30分間ブレインキュベーションを行った。

【0091】その後、試験管あたり1mMの1-パルミトイル-2-[1-¹⁴C]アラキドニルホスファチジルコリン(Dupont社製)と、25mMのデオキシコレートNa塩を含む80%エタノール溶液50μlを加え、37℃で5分間インキュベートした。200mMのエチレンジアミン4酢酸を含む5%トリトンX-100を100μl加え反応を停止させた。0.1%酢酸/n-ヘキサンを5ml、無水硫酸ナトリウムを約0.25g加え、10分間振とうした。3,000rpmで10分間遠心分離後、上層のn-ヘキサン層1mlをバイアルに移し放射能量を液体シンチレーションカウンターで測定した。

【0092】次にII型PLA₂に対する阻害作用は、デハースらの方法[Biochemistry, 13, 1146, (1974)]に基づき、以下の方法で測定した。エッペンドルフ型チューブに塩化カルシウム10mMを含む0.1Mトリス-塩酸緩衝液(pH7.5)に、精製水またはジメチルスルホキシド50μlに溶解した検体を終濃度が10、100、500μMとなるように加え、これに部分精製したヒトのリウマチ関節炎液由来のPLA₂(比活性0.

128nmol/30分/50ng蛋白質)を添加し、37℃で30分間ブレインキュベーションを行った。その後、トリチウム標識アラキドン酸でラベルした大腸菌菌体(Dupont社製)をチューブあたり0.71nmol Pi、約30,000dpmを50μlの生理食塩水に懸濁して加え、37℃で30分間インキュベーションを行った。2.5N-塩酸を100ml添加し反応を停止させ、33.3mg/mlのウシ血清アルブミンを300μl加えた後、14,000rpm、5分間遠心分離し、遠心上清450μlをバイアルに移し放射能量を液体シンチレーションカウンターで測定した。I型、II型に対する阻害活性が強い場合は、検体濃度を0.1、1、10μMあるいはより低濃度に調製し測定した。

【0093】これらの方法で測定した化合物のPLA₂阻害活性のIC₅₀値を表-1[表1]に示した。本表において、実施例番号39、40等の化合物は、いわゆるプロドラッグ体であり、本試験によるPLA₂阻害活性値は低い。しかし、薬物を体内に投与した場合、エステラーゼ等の酵素でエステル部位が速やかに加水分解され、相当する活性体(実施例番号7、33)に変換し、強いPLA₂阻害活性を示す。

【0094】

【表1】

表-1 PLA₂阻害活性のIC₅₀値

実施例 番号	IC ₅₀ 値 (μM)	
	I型PLA ₂	II型PLA ₂
2	46	3.7
4	2.6	0.38
6	1.4	5.4
7	5.4	0.32
9	2.4	0.24
11	4.5	0.028
13	38	0.015
15	4.0	0.78
17	3.6	10.0
19	2.0	4.9
20	16	3.0
22	26	27.0
23	40	10.0
25	14	0.75
26	40	2.6
27	44	1.7
28	58	3.8
29	1.8	0.03
30	2.3	0.4
31	8.1	5.6
33	2.0	0.20
34	11	1.50
35	2.7	0.40
36	19.2	16.7
37	21	4.40
38	142	8.1
39	175	>500
40	360	>500

【0095】実施例44 抗肺炎作用（セルレイン誘発急性肺炎モデル）

実験には、雄性SDラット（日本エスエルシー、9週齢、体重280～300g）を用いた。実験前日に大腿静脈にカニューレを挿入し、前日夕方より絶食した。セルレイン（Bachem社から購入）は、生理的食塩水に溶解し、20μg/kg（2ml/kg）を1時間おきに4回、頸背部に皮下投与した。検体は5%マンニトール水溶液に懸濁後、酢酸ナトリウムまたは1N KOHを添加、溶解して投与した。他の対照化合物も5%マンニトールに溶解後、検体と同様に酢酸ナトリウムまたは1N KOHを添加して検体溶液と等しいpHに調整して投与した。

【0096】病態対照群には溶媒（5%マンニトールに酢酸ナトリウムまたは1N KOHを添加して検体溶液と

等しいpHに調整した溶液）のみ投与した。薬物投与は、カニューレを通してセルレイン投与開始と同時に開始し、0.8ml/hrの流量で5時間infusionを行った。なお、セルレイン投与開始前には薬物の血中濃度を上昇させる目的で、それぞれの薬物を溶媒のみで溶解したものの1時間分をカニューレを通して投与した。

【0097】セルレイン薬物投与開始から5時間後にネンブタール過剰投与により犠死せしめ、脾臓を摘出し、その湿重量を測定した。薬物投与群におけるこの湿重量の値が少ないほど抗肺炎作用が強いと考えられる。[図1]に代表的な検体についての結果を示すが、本発明化合物は概ねこれらの作用を有する。

【0098】

【発明の効果】一般式（1）で表される安息香酸誘導体

は、実施例で詳しく述べたとおりI型およびII型PLA₂に対する強い阻害活性を有しており、肺炎、リウマチ、アレルギー、虚血性血管障害、気管支喘息、潰瘍、関節炎、皮膚炎、痛風、外傷誘発炎症などの炎症性疾患の予防および/または治療薬として有用である。

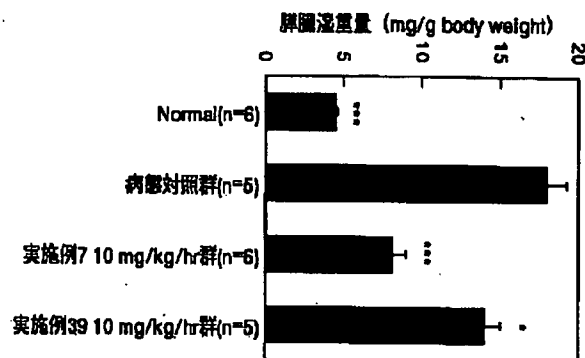
【図面の簡単な説明】

【図1】ラットセルレイン誘発急性肺炎モデルにおける抗肺炎作用を示す図である。

【符号の説明】

* 有意水準 $p < 0.01$
 *** 有意水準 $p < 0.001$
 I 標準偏差

【図1】



フロントページの続き

(51)Int. Cl. ⁶	識別記号	庁内整理番号	F I	技術表示箇所	
A 6 1 K 31/60	ACD		A 6 1 K 31/60	ACD	
	AC J			AC J	
	ACL			ACL	
	ADA			ADA	
	ADM			ADM	
C 0 7 C 65/21		9450-4H	C 0 7 C 65/21	D	
	205/57	9450-4H		205/57	
	219/14	7457-4H		219/14	
	229/62	9450-4H		229/62	
	233/54			233/54	
	235/46	9547-4H		235/46	
	311/08	7419-4H		311/08	
	317/44	7419-4H		317/44	
	321/24	7419-4H		321/24	
	323/50	7419-4H		323/50	
(72)発明者 依田 洋恵	千葉県茂原市東郷1144番地 三井東圧化学株式会社内		(72)発明者 大塚 健悟	千葉県茂原市東郷1144番地 三井東圧化学株式会社内	
(72)発明者 深澤 信幸	千葉県茂原市東郷1144番地 三井東圧化学株式会社内		(72)発明者 川面 博	千葉県茂原市東郷1900番地の1 三井東圧化学株式会社内	
(72)発明者 國分 裕一郎	千葉県茂原市東郷1900番地の1 三井東圧化学株式会社内		(72)発明者 國分 裕一郎	千葉県茂原市東郷1900番地の1 三井東圧化学株式会社内	

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 707 007 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
12.12.2001 Bulletin 2001/50

(51) Int Cl.7: C07D 405/12, C07D 311/64,
C07D 311/58, C07D 213/38,
C07D 333/20, C07C 211/27,
A61K 31/44, A61K 31/35

(21) Application number: 95115779.1

(22) Date of filing: 06.10.1995

(54) (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chromane as CNS active agent

ZNS wirksames (R)-(-)-2-[5-(4-Fluorophenyl)-3-pyridylmethylaminomethyl]chroman

(R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhy]chromane agissant sur le système nerveux central

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE
Designated Extension States:
LT LV SI

(56) References cited:
EP-A- 0 145 067 WO-A-93/17017
WO-A-95/05383 DE-A- 2 364 685
DE-A- 4 135 474 DE-A- 4 226 527

(30) Priority: 14.10.1994 EP 94116223

(43) Date of publication of application:
17.04.1996 Bulletin 1996/16

(60) Divisional application:
01109746.6 / 1 123 933

(73) Proprietor: MERCK PATENT GmbH
64293 Darmstadt (DE)

(72) Inventors:

- Böttcher, Henning, Dr.
D-64287 Darmstadt (DE)
- Devant, Ralf, Dr.
D-64293 Darmstadt (DE)
- Greiner, Hartmut, Dr.
D-64331 Weiterstadt (DE)
- Bartoszyk, Gerd
D-64331 Weiterstadt (DE)
- Berthelon, Jean-Jacques, Dr.
F-69005 Lyon (FR)
- Noblet, Marc
F-69008 Lyon (FR)
- Zeiller, Jean-Jacques
F-69100 Villenbonne (FR)
- Brunet, Michel
F-69780 Toussieu (FR)

- CHEMICAL AND PHARMACEUTICAL BULLETIN., vol.24, no.11, 1976, TOKYO JP pages 2661 - 2667 N. HIROSE ET AL. 'Studies on benzoheterocyclic derivatives. XVI. Synthesis and analgesic action of benzofuran derivatives.'
- CHIMICA TERAPEUTICA., vol.8, no.3, 1973, FR pages 259 - 270 C. GOLDENBERG ET AL. 'Benzofuran series. XLIX. Synthesis of aralkyl- and aryloxyalkyl(2,3-dihydro-2-benzofuryl)methylamines and related structures.'
- CHEMICAL ABSTRACTS, vol. 70, no. 7, 17 February 1969, Columbus, Ohio, US; abstract no. 28816q, H. SHOJI ET AL. '2-(Substituted aminomethyl)-2,3-dihydrobenzofurans.' page 308 ; & JP-A-68 018 131 (EISAI CO., LTD.)
- CHEMICAL ABSTRACTS, vol. 94, no. 13, 30 March 1981, Columbus, Ohio, US; abstract no. 103390x, H. TAKIZAWA ET AL. 'Substituted ethanolamines.' page 749 ; & DE-A-30 10 752 (KYOWA HAKKO KOGYO CO., LTD.)
- CHEMICAL AND PHARMACEUTICAL BULLETIN., vol.30, no.11, 1982, TOKYO JP pages 4092 - 4101 T. FUJIKURA ET AL. 'Studies on benzenesulfonamide derivatives with alpha- and beta-adrenergic antagonistic and antihypertensive activities.'

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 707 007 B1

- CHEMICAL ABSTRACTS, vol. 86, no. 21, 23 May 1977, Columbus, Ohio, US; abstract no. 150434j, R.C. SAXENA ET AL. 'Effect of nicotine administration into the lateral cerebral ventricles of mice provides evidence for cholinergic mechanisms in the CNS.' page 27 ; & DRUGS AND CENTRAL SYNAPTIC TRANSMISSION, PAPERS OF A SYMPOSIUM, 1976, SASINGSTOKE, GB pages 139 - 144
- CHEMICAL ABSTRACTS, vol. 72, no. 21, 25 May 1970, Columbus, Ohio, US; abstract no. 109472t, J.H. OLIVER ET AL. 'Effect of reserpine and other drugs on the CNS and lethal effects of hyperbaric oxygen in mice.' page 224 ; & ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE., vol.183, no.2, 1970, GHENT, BELG. pages 215 - 223

- PATENT ABSTRACTS OF JAPAN vol. 18, no. 19 (C-1152) 13 January 1994 & JP-A-05 255 302 (YAMANOUCHI PHARMACEUTICAL CO., LTD.) 5 October 1993

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

[0001] The invention relates to (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts thereof.

[0002] The object of the invention was to find novel compounds capable of being used for the preparation of drugs.

[0003] It has been found that (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible acid addition salts possess valuable pharmacological properties. Thus, in particular, it is active on the central nervous system, especially as serotonin agonist and antagonist. It inhibits the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., *European J. Pharmacol.* **140** (1987), 143-155). It also modifies the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphe (Seyfried et al., *European J. Pharmacol.* **160** (1989), 31-41). It also has analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, *Proc. Soc. Exptl. Biol. Med.* **104** (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds. It is also useful for prophylaxis and control of the sequelae of cerebral infarction (Apoplexia cerebri) such as stroke and cerebral ischaemia.

The substance can be used in the treatment of diseases which are related to interferences in the serotonergic and dopaminergic systems and which involve the receptors with high affinity to the 5-hydroxytryptamin (5HT1A type) or/and dopamin (D2 type) receptors.

[0004] It is suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depression states, sexual dysfunctions caused by the central nervous system, disturbances in sleep or absorption of food. Furthermore, it is suitable to eliminate cognitive deficiencies, to improve powers of learning and memory and to treat Alzheimer's disease. They are also suitable for psychosis (schizophrenia).

(R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible acid addition salts can therefore be used as active ingredient for anxiolytics, antidepressants, neuroleptics, and/or antihypertensives, and also as intermediate for the preparation of other pharmaceutical active ingredients.

[0005] The invention relates to (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and to its biocompatible acid addition salts.

[0006] The invention further relates to a process for the preparation of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its salts, characterized in that 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with (R)-2-aminomethyl-chromane and/or in that the resulting base is converted into one of its salts by treatment with an acid.

[0007] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, *Methoden der Organischen Chemie* (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane.

[0008] The reaction of the educt compounds proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component. The reaction time is between a few minutes and 14 days, depending on the conditions used, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

[0009] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane possesses one centre of asymmetry. When prepared, it can therefore be obtained as racemate or else in the optically active form if optically active starting materials are used.

[0010] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e.g. sulphuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i.e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulphonic or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethy-

lactic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedithiophonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemono-sulphonic and naphthalenedithiophonic acids and laurylsulphuric acid.

[0011] The invention further relates to the use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, it can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

[0012] The invention further relates to compositions, especially pharmaceutical preparations, containing (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and/or one of its biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compound can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

[0013] The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

[0014] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. It can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with a-methylidopa). The compound can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially

in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (Apoplexia cerebri), such as stroke and cerebral ischaemia.

5 Furthermore, it is suitable to eliminate cognitive deficiencies, to improve the power of learning and memory and to treat Alzheimer disease.

[0015] In these treatments, (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocomin), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

[0016] In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C.

Preparation example

[0017] A solution of 2.8 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 2.2 g 3-(chloromethyl)-pyridine in 250 ml of DMF are stirred together with 1 g N-methylmorpholine for 12 hours at 20° and worked up in a conventional manner to give N-(3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 163-164°.

Preparation of the enantiomeric compound:

Example

[0018] A solution of 4.5 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 3.9 g tosylproline in 190 ml ethanol are refluxed for 15 minutes. Afterwards the solution is cooled down to 5° while it is stirred. During the cooling

procedure a few crystals of pure (R)-2-aminomethyl-chromane were added. The solution was kept under stirring at 5° for a period of 18 hours and afterwards the pure enantiomer (R)-2-aminomethyl-chromane was separated. The crystallisation process was repeated two times with the crystals derived from the first crystallisation in order to yield an enantiomeric excess of more than 99 %.

[0019] Subsequently the (R)-2-aminomethyl-chromane was reacted with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Preparation example to give (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane [= (R)-(-)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine]. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 234-235°; $[\alpha]^{20}_D = -65^\circ$ (c = 1, methanol). The examples below relate to pharmaceutical preparations.

Example A: Injection vials

[0020] A solution of 100 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and 5 g of disodium hydrogenphosphate in 31 of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are closed in a sterile manner. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

[0021] A mixture of 20 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is fused with 100 g of soya lecithin and 1400 g of cocoa butter, and the mixture is poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

[0022] A solution of 1 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of doubly distilled water. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

[0023] 500 mg of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is mixed with 99.5 g of petroleum jell under aseptic conditions.

Example E: Tablets

[0024] A mixture of 100 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane, 1 kg of lactose, 600 g of microcrystalline cellulose, 600 g of maize starch, 100 g of polyvinyl-pyrrolidone, 80 g of talc and 10 g of magnesium stearate is pressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

[0025] Tablets are pressed as stated in Example E and then coated in a customary manner with a coating of sucrose, maize starch, talc, tragacanth and colorant.

Example G: Capsules

[0026] Hard gelatin capsules are filled with (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane in the customary manner, so that each capsule contains 5 mg of active compound.

Example H: Inhalation spray

[0027] 14 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray burst (about 0.1 ml) corresponds to a dose of about 0.14 mg.

Claims

1. (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts thereof.
2. A process for the preparation of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane and its salts, **characterized in that** 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with (R)-2-aminomethyl-chromane, and/or **in that** the resulting base is converted into one of its salts by treatment with an acid.
3. Process for the manufacture of pharmaceutical preparations, **characterised in that** (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane and/or one of its biocompatible salts are converted into a suitable dosage form together with at least one solid, liquid or semiliquid excipient or adjunct.
4. Pharmaceutical preparation, **characterised in that** it contains (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and/or one of its biocompatible salts.

5. Use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane or its biocompatible salts for the manufacture of a drug.
6. Use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane or its biocompatible salts, for the manufacture of a pharmaceutical for the treatment of disorders of the central nervous system.
7. Use according to claim 6 in which the disorders of the central nervous system are anxiety, depression states, Alzheimer's disease or schizophrenia.

Patentansprüche

1. (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und physiologisch unbedenkliche Salze davon.
2. Verfahren zur Herstellung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und Salzen davon, **dadurch gekennzeichnet, daß** man 3-(Chlormethyl)-5-(4-fluormethyl)pyridin mit (R)-2-Aminomethylchroman umsetzt, und/oder die so erhaltene Base durch Behandlung mit einer Säure in eines ihrer Salze umwandelt.
3. Verfahren zur Herstellung von pharmazeutischen Zubereitungen, **dadurch gekennzeichnet, daß** man (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und/oder eines seiner biokompatiblen Salze zusammen mit wenigstens einem festen, flüssigen oder halbflüssigen Hilfsmittel bzw. Zusatzstoff in eine geeignete Dosierungsform bringt.
4. Pharmazeutische Zubereitung, **dadurch gekennzeichnet, daß** sie (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und/oder eines seiner biokompatiblen Salze enthält.
5. Verwendung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman oder biokompatiblen Salzen davon zur Herstellung eines Arzneimittels.
6. Verwendung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman oder biokompatiblen Salzen davon zur Herstellung eines Medikaments zur Behandlung von Erkrankungen des zentralen Nervensystems.
7. Verwendung gemäß Anspruch 6, wobei es sich bei den Erkrankungen des zentralen Nervensystems um Angstzustände, Depression, Alzheimer-Krankheit oder Schizophrenie handelt.

Revendications

1. (R)-(-)-2-[5-(4-Fluorophényl)-3-pyridylméthylaminométhyl]-chromane et ses sels acceptables d'un point de vue physiologique.
2. Procédé de préparation du (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane et de ses sels, **caractérisé en ce que** l'on fait réagir la 3-(chlorométhyl)-5-(4-fluorométhyl)pyridine avec le (R)-2-aminométhylchromane, et/ou **en ce que** l'on transforme la base résultante en un de ses sels par traitement avec un acide.
3. Procédé de fabrication de préparations pharmaceutiques, **caractérisé en ce que** le (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane et/ou un de ses sels biocompatibles sont mis sous une forme d'administration appropriée en même temps qu'au moins un excipient ou additif solide, liquide ou semi-liquide.
4. Préparation pharmaceutique, **caractérisée en ce qu'elle** contient du (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]-chromane et/ou un de ses sels biocompatibles.
5. Utilisation de (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane ou de ses sels biocompatibles pour la fabrication d'un médicament.
6. Utilisation de (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane ou de ses sels biocompatibles pour la fabrication d'un produit pharmaceutique destiné au traitement de troubles du système nerveux central.
7. Utilisation selon la revendication 6 dans laquelle les troubles du système nerveux central sont l'anxiété, les états dépressifs, la maladie d'Alzheimer ou la schizophrénie.

(12) UK Patent Application (19) GB (11) 2 278 054 (13) A

(43) Date of A Publication 23.11.1994

(21) Application No 9310199.6

(22) Date of Filing 18.05.1993

(71) Applicant(s)
Zeneca Limited

(Incorporated in the United Kingdom)

Imperial Chemical House, 9 Millbank, LONDON,
SW1P 3JF, United Kingdom

(72) Inventor(s)
Thomas Lee Grant
Martin Howdle Todd
Keith Hopkinson Gibson
Cyrus John Ohnmacht
Keith Russell

(74) Agent and/or Address for Service
Martin Alexander Hay
Imperial Chemical Industries PLC, ICI Group Patents,
Group Patents Services Dept, PO Box 6, Shire Park,
Bessemer Road, WELWYN GARDEN CITY,
Hertfordshire, AL7 1HD, United Kingdom

(51) INT CL⁵
A61K 31/165

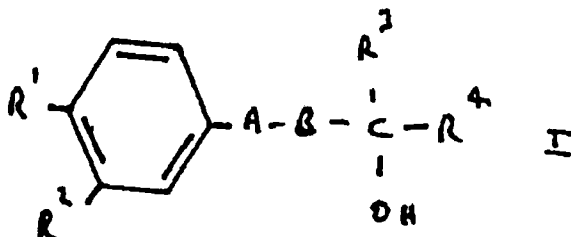
(52) UK CL (Edition M)
A5B BHA B170 B180 B42Y B420 B422 B48Y B480 B482
B484 B485 B49Y B492 B493 B58Y B586 B59Y B596
B64Y B642 B645 B822 B823 B828 B829 B839 B842
U1S S2414

(56) Documents Cited
GB 2102287 A

(58) Field of Search
UK CL (Edition M) A5B BHA BJA
INT CL⁵ A61K 31/085 31/135 31/165 31/275
ON-LINE DATABASES: CAS-ONLINE

(54) Compounds for the treatment of urinary incontinence

(57) Compounds of formula I



wherein:

(a) one of R¹ and R² represents (1-4C)alkyl, {(1-4C)alkyl}[(1-4C)alkanoyl]amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R¹ and R² represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl;

(b) -A-B- is selected from NHCO, OCH₂, NHCH₂, trans- vinylene and ethynylene

(c) R³ and R⁴ are independently (1-3C)alkyl substituted by atoms selected from fluoro and chloro or R³ and R⁴, together with the carbon atom to which they are attached, form a 3 to 5 membered cycloalkyl ring optionally substituted with fluorine atoms.

(d) a pharmaceutically acceptable in vivo ester or compound I.

The compounds are potassium channel openers and are useful for the treatment of urinary incontinence.

THERAPEUTIC COMPOUNDS

This invention relates to the use of certain compounds in the treatment of bladder instability in mammals such as man and as potassium channel openers.

It is known that bladder tissue is excitable and that urinary incontinence can be caused by uncontrolled or unstable bladder contractions.

It has now been found that certain compounds (some of which are disclosed in EP-A1-2892 as anti-androgens) are unexpectedly capable of relaxing bladder smooth muscle, thus preventing or ameliorating uncontrolled or unstable bladder contractions. Hence, the compounds may be useful for the treatment of urge incontinence, which includes for example detrusor instability, which may result from cystitis, urethritis, tumors, stones, diverticuli or outflow obstruction; and detrusor hyperreflexia, which may result from stroke, dementia, Parkinsons, suprasacral spinalcord injury or suprasacral spinalcord disease.

This invention provides the use of a compound of formula I (formula set out, together with other formulae referred to by Roman numerals, at the end of this specification), wherein:

one of R^1 and R^2 represents (1-4C)alkyl, {(1-4C)alkyl}{(1-4C)alkanoyl}amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R^1 and R^2 represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl;

A-B is selected from $NHCO$, OCH_2 , $NHCH_2$, trans-vinylene and ethynylene;

R^3 and R^4 are independently (1-3C)alkyl substituted by from 0 to $2k+1$ atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said (1-3C)alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4 , together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to $2m-2$ fluorine atoms wherein m is the number of carbon atoms in said ring;

or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I;

or a pharmaceutically acceptable salt of said compound or said ester in the manufacture of a medicament for the treatment of urinary incontinence.

The invention further provides a method for the treatment of urinary incontinence, comprising administering to a mammal (including man) in need of such treatment an effective amount of an amide of formula I as defined above, or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I or a pharmaceutically acceptable salt of said compound or said ester.

The invention also provides those compounds of formula I, and the in vivo hydrolysable esters and pharmaceutically acceptable salts thereof that are novel.

The invention further provides a pharmaceutical composition comprising a novel compound of formula I as defined above, or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I or a pharmaceutically acceptable salt of said compound or said ester, and a pharmaceutically acceptable diluent or carrier.

In this specification the terms "alkyl" and "alkoxy" include both straight and branched chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

The term "halo" is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

It will be appreciated by those skilled in the art that certain compounds of formula I contain an asymmetrically substituted carbon atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit

polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of urinary incontinence, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the treatment of urinary incontinence by the standard tests described hereinafter.

The use of compounds in the form of the (S)-enantiomer is preferred.

Particular values for a substituent represented by R^1 are hydrogen, methyl, ethylacetyl amino, methanesulphonyl, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, cyclohexylsulphonyl, phenylthio and benzylsulphonyl.

Particular values for a substituent represented by R^2 are hydrogen, ethylacetyl amino, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl and phenylthio.

Examples of values for R^1 and R^2 together with the phenyl group to which they are attached are 4-methylphenyl, 4-ethylacetylphenyl, 3-chloro-4-methanesulphonylphenyl, 4-nitrophenyl, 3-phenylthio-4-nitrophenyl, 3-chloro-4-nitrophenyl, 3-trifluoromethyl-4-nitrophenyl, 4-cyanophenyl, 3,4-dicyanophenyl, 3-chloro-4-cyanophenyl, 3-trifluoromethyl-4-cyanophenyl, 3-cyanophenyl, 4-chloro-3-ethylacetylaminophenyl, 4-bromo-3-trifluoromethylphenyl, 4-cyclohexylsulphonylphenyl, 3,4-dichlorophenyl and 4-benzylsulphonylphenyl.

Preferably A-B represents $NHCO$, OCH_2 , trans-vinylene or ethynylene. Most preferably it represents $NHCO$, trans-vinylene or ethynylene.

Preferably either R^3 and R^4 both represent difluoromethyl, or R^4 represents trifluoromethyl and R^3 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl. More preferably R^4 represents trifluoromethyl and R^3 represents methyl.

A compound of formula I can be made by processes which include processes known in the chemical arts for the production of structurally analogous compounds. In respect of novel compounds of formula I, such processes are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as given above unless otherwise qualified. Such a process can be effected, generally,

(a) by deprotecting a protected compound of formula II wherein "Pg" is a suitable alcohol protecting group, such as for example a benzyl group or a silyl protecting group; Examples of suitable reagents for deprotecting an amide of formula II when Pg is benzyl are (1) hydrogen in the presence of palladium-on-carbon catalyst, i.e. hydrogenolysis; or (2) hydrogen bromide or iodide; and when PG is a silyl protecting group are (1) tetrabutylammonium fluoride; or (2) aqueous hydrofluoric acid. The reaction can be conducted in a suitable solvent such as ethanol, methanol, acetonitrile, or dimethylsulfoxide and may conveniently be performed at a temperature in the range of -40 to 100 °C.

(b) for a compound of formula I in which A-B is NHCO, by coupling an aniline of formula III with an acid of formula IV. The reaction can be conducted in a suitable solvent and in the presence of a suitable coupling reagent. Suitable coupling reagents generally known in the the art as standard peptide coupling reagents can be employed, for example thionyl chloride, carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40 °C;

(c) for a compound of formula I in which A-B is ethynylene, by reacting a corresponding alkyne of formula V with a base such as lithium diisopropylamide (LDA), n-butyllithium or tert-butyllithium, followed by treatment with a ketone of formula R^3-CO-R^4 . The reaction may conveniently be performed at a temperature in the range of -100 to -40 °C preferably at a temperature in the range of -70 to -40 °C and

in a solvent such as tetrahydrofuran (THF), diethyl ether, or 1,2-dimethoxyethane (DME).

(d) for a compound of formula I in which A-B is trans-vinylene, by reducing a corresponding compound of formula I in which A-B is ethynylene with a suitable reducing agent, for example lithium aluminum hydride or sodium bis(methoxyethoxy)aluminum hydride. The reaction can be conducted in a suitable solvent such as THF or diethyl ether, and at a temperature in the range of 0 to 50 °C.

(e) for a compound of formula I in which A-B is tran-vinylene, by dehydration of a diol of formula VI in the presence of an acid catalyst (for example p-toluenesulfonic acid), neat or with a solvent such as toluene or dichloromethane, or a strong base (for example sodium hydride) in a solvent such as tetrahydrofuran and at a temperature in the range of 0 to 200 °C preferably a temperature in the range of 20 to 100 °C.

(f) for a compound of formula I in which A-B is trans-vinylene, by base catalyzed opening of an epoxide of formula VII. The opening may be carried out in a suitable organic solvent such as for example, ethers, alcohols, or toluene; ethers such as tetrahydrofuran are preferred. Suitable bases include for example sodium hydroxide, sodium methoxide, potassium tert-butoxide or sodium hydride. A basic aqueous solution may conveniently be employed. A preferred base is aqueous sodium hydroxide. The opening may be carried out at a temperature in the range of -50 °C to 100 °C, preferably at a temperature in the range of 0 to 50 °C, such as for example room temperature.

(g) for a compound of formula I in which A-B is NHCH_2 , by reducing a corresponding compound of formula I in which A-B is NHCO , with a suitable reducing agent such as lithium aluminum hydride or borane. The reaction can conveniently be carried out at a temperature in the range of 0 °C to reflux, in solvents such as for example diethyl ether, THF, or DME.

(h) for a compound of formula I in which A-B is OCH_2 , by reacting an ethylene oxide of formula VIII with a corresponding compound of formula IX (wherein J is, correspondingly, oxygen), in the presence of a base such as for example sodium hydride. The reaction

can be conducted at reflux in a solvent such as methylene dichloride.

If not commercially available, the necessary starting materials for the procedures such as that described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples.

In general, a compound of formula II in which A-B is OCH_2 or NHCH_2 may be made by treating a corresponding compound of formula IX wherein J is oxygen or NH with a corresponding compound of formula X (wherein Pr is a protective group such as silyl and X is a suitable leaving group such as for example mesylate or triflate), in the presence of a base such as an alkali metal hydride (e.g., sodium hydride), in a solvent such as THF, DMF, DMSO, or DMPU, and at a temperature of about 20 °C to about reflux. A compound of formulae II, wherein A-B is NHCO , may be made in a manner analogous to that described in procedure (b) above; that is, by coupling a corresponding aniline with a corresponding acid. The protected acid may be made by a conventional procedure, for example by (i) esterifying an acid of formula IV by means of a conventional esterification procedure such as reaction with a lower alcohol (e.g., methanol) in the presence of an acid catalyst (for example sulfuric acid); (ii) reaction of the ester thus formed with an agent which provides the protecting group Pg, such as benzyl chloride (to provide a benzyl protecting group) or any of the conventional silylating agents known and used for such purpose (such as 2-trimethylsilylethoxymethyl chloride, SEM, in the presence of a suitable base such as sodium hydroxide or triethylamine optionally in the presence of a catalyst such as DMAP); and (iii) cleavage of the ester group under mild alkaline conditions (i.e., employing a base such as potassium carbonate) to yield the desired protected acid.

A compound of formula V may be made by reacting a corresponding compound of formula XI, wherein L is bromo or iodo, with trimethylsilylacetylene in the presence of a catalyst such as a combination of bis(triphenylphosphine)palladium dichloride and

copper(I) iodide in diethylamine or triethylamine, followed by treatment with a base (for example, an alkali metal hydroxide such as sodium or lithium hydroxide) in a lower alcohol as solvent to effect removal of the trimethylsilyl group.

A compound of formula VIII may be made by treating a corresponding ketone having the formula R^3-CO-R^4 with the ylide derived from the reaction of a trimethylsulfonium salt (such as trimethylsulfonium iodide) with a base (such as an alkali metal hydroxide). The reaction may be conducted in a one-pot process employing a solvent such as dichloromethane.

A compound of formula IX, wherein J is oxy, may be made by diazotizing a corresponding aniline of formula XI, wherein L is amino, as previously discussed, and heating in dilute sulfuric acid to form the corresponding phenol.

A compound of formula X, wherein X is mesylate, may be made by (1) esterifying an acid of formula IV; (2) protecting the alcohol group, by treating with for example trimethylsilyl chloride in a solvent such as dichloromethane and at a temperature of from about -78 to about 25 °C; (3) treating the protected compound thus obtained with a suitable reducing agent such as lithium aluminum hydride in a solvent such as diethyl ether or THF and at a temperature of about 0 to about 25 °C, thereby reducing the carbonyl group to methylene; followed by (4) treating the reduced product with trifluoromethylsulfonic anhydride in the presence of a base such as triethylamine, in a solvent such as dichloromethane, and at a temperature of about -78 °C to about 25 °C.

An epoxide of formula VII may be prepared from a diol of formula VI using a suitable dehydrating agent, for example bis[α,α -bis(trifluoromethyl)benzenemethanolato]diphenylsulphur. A diol of formula VI may be prepared from a compound of formula I, wherein A-B is $CHCO$, by reduction. The reduction may be carried out using a suitable reducing agent, for example a hydride, such as sodium borohydride.

A compound of formula I, wherein A-B is $CHCO$, may be prepared from a compound of formula XI, wherein L is methyl, by deprotonation and treatment with an amide of formula XII, in which R^6

and R⁷ are each independently lower alkyl, or in which R⁶ and R⁷ when taken together with the atoms to which they are attached form a 5-7 membered ring. The deprotonation of the toluene may be carried out with a suitable base, for example lithium diisopropyl amide. The reaction may be carried out in a suitable organic solvent, for example, an ether such as tetrahydrofuran. The reaction may be carried out at a suitable temperature, for example a temperature in the range of -78 °C to 100 °C.

An amide of formula XII may be prepared from an acid of formula IV, or a reactive derivative thereof, by reaction with the corresponding amine.

In cases where compounds of formula I are sufficiently basic or acidic to form stable acid or basic salts, administration of the compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following. Examples of suitable pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiologically acceptable anion, for example, tosylate, methanesulfonate, acetate, tartrate, citrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed such as sulfate, nitrate, and hydrochloride.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound of formula I (or its ester) with a suitable acid affording a physiologically acceptable anion. It is also possible with most compounds of the invention to make a corresponding alkali metal (e.g., sodium, potassium, or lithium) or alkaline earth metal (e.g., calcium) salt by treating an amide of formula I (and in some cases the ester) with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g. the ethoxide or methoxide in aqueous medium followed by conventional purification techniques.

In vivo hydrolyzable esters of compounds of the invention may be made by coupling with a pharmaceutically acceptable carboxylic acid or an activated derivative thereof. For example, the coupling

may be carried out by treating a parent amide of formula I with an appropriate acid chloride (for example, acetyl chloride, propionyl chloride, or benzoyl chloride) or acid anhydride (for example, acetic anhydride, propionic anhydride, or benzoic anhydride) in the presence of a suitable base such as triethylamine. Those skilled in the art will appreciate that other suitable carboxylic acids (including their activated derivatives) for the formation of in vivo hydrolyzable esters are known to the art and these are also intended to be included within the scope of the invention. Catalysts such as 4-dimethylaminopyridine may also be usefully employed.

When used to treat urinary incontinence, a compound of formula I is generally administered as an appropriate pharmaceutical composition which comprises a compound of formula I as defined hereinbefore together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such compositions are provided as a further feature of the invention.

The compositions may be obtained employing conventional procedures and excipients and binders and may be in a variety of dosage forms. For example, they may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of suppositories for rectal administration; in the form of sterile solutions or suspensions for administration by intravenous, intravesicular, subcutaneous or intramuscular injection or infusion; or in the form of a patch for transdermal administration.

Treatment using a compound according to the invention may be remedial or therapeutic as by administering a compound following the onset or development of urinary incontinence in a patient. Treatment may also be prophylactic or prospective by administering a compound in anticipation that urinary incontinence may develop, for example in a patient who has suffered from incontinence in the past.

According to a further aspect, the invention provides the use of a compound of formula I, as defined hereinabove, in the manufacture of a medicament for the treatment of urinary incontinence.

It has also unexpectedly been found that compounds according to the invention are potassium channel openers. It is known that by

functioning to open potassium channels, potassium channel opening compounds may thereby function to relax smooth muscle.

Because compounds according to the invention function to open cell potassium channels, they may also be useful as therapeutic agents in the treatment of other conditions or diseases in which the action of a therapeutic agent which opens potassium channels is desired or is known to provide amelioration. Such conditions or diseases include hypertension, asthma, peripheral vascular disease, right heart failure, congestive heart failure, angina, ischemic heart disease, cerebrovascular disease, renal colic, disorders associated with kidney stones, irritable bowel syndrome, male pattern baldness, premature labor, and peptic ulcers.

According to another aspect therefore, the invention provides the use of a compound of formula I, or an in vivo hydrolysable ester thereof or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or condition in which the action of a potassium channel opener is required.

The dose of compound of formula I which is administered will necessarily be varied according to principles well known in the art taking account of the route of administration, the severity of the incontinence condition, and the size and age of the patient. In general, a compound of formula I will be administered to a warm blooded animal (such as man) so that an effective dose is received, generally a daily dose of above 0.005, for example in the range of about 0.01 to about 10 mg/kg body weight.

It will be apparent to those skilled in the art that a compound of formula I may be co-administered with other therapeutic or prophylactic agents and/or medicaments that are not medically incompatible therewith. Compounds within the scope of the invention have not been found show any indication of untoward side-effects in laboratory test animals at several multiples of the minimum effective dose.

The actions of compounds of formula I as smooth muscle relaxants useful as therapeutic agents for the treatment of urinary incontinence through their action to open potassium channels and

hyperpolarize the membrane electrical potential in bladder detrusor smooth muscle may be shown using suitably designed in vitro tests, such as the one described following. Compounds according to the invention typically exhibit an IC_{50} on the order of 30 micromolar or less in the test. " IC_{50} " is a well understood term and means the concentration of test compound which causes a 50% decrease in the in vitro contraction of the bladder tissue described in the following test.

Male albino Hartley guinea pigs (450-500g) are sacrificed by carbon dioxide induced asphyxiation and quickly exsanguinated. The lower abdominal cavity is opened and the urinary bladder isolated. The bladder is cleaned of surrounding connective and adipose tissue, and the portion above the ureteral orifices is removed and washed in Krebs-Henseleit buffer solution of the following composition (in mM): NaCl 118.0, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25.0 and d-glucose 11.1. The solution is warmed to 37°C and gassed with 95% O_2 and 5% CO_2 . With vigorous bubbling, the solution should have a pH value close to 7.4.

The dome of the washed bladder is cut off and discarded; the remaining bladder is placed on a gauze in a Petri dish containing the buffer solution. A mid-ventral longitudinal cut is made with scissors to open the bladder. The strips cut from the dome and the base edge are discarded. The remaining detrusor mid-section is cut into two horizontal strips with an approximate width of 2.0 mm. These two strips are further bisected at the mid-dorsal section, creating four strip of similar dimensions. Each strip thus contains both dorsal and ventral portions of the bladder.

The two ends of each individual strip are tied to a glass support rod and a force-displacement transducer (Grass model FT03), respectively, with 4-0 black braided silk suture.

The transducers are connected to a polygraph (Grass model 7E), which is calibrated at 5 mV/cm and the calibration checked for linearity with weights of 5 and 0.5 grams. The analog electrical output signals from the polygraph are digitized by a Modular Instrument Micro 5000 signal processing system using Biowindow Data Acquisition Software, which is run under the Microsoft OS/2 operating

system with an IBM-compatible PC.

The detrusor strips on the glass rod are secured in 20 ml tissue baths and allowed to equilibrate under a preload tension of 2 grams. During the following 45 to 60 min equilibration period, the tissue is washed with fresh buffer solution at 15 min interval, with the tension adjusted, if necessary, to 2 grams prior to washing. After the equilibration period, a priming dose of 15 mM KCl (total concentration in the bath) is applied. The tissue is washed after 10 min and washed twice more at 15 min intervals with tension adjusted to 2 grams before each washing.

When the tissue relaxes to a steady state after the final washing, 15 mM KCl is again applied. Once the myogenic activity of the tissue reaches a steady state, the baseline data are acquired through the Biowindows Data Acquisition System by averaging 5 min of the myogenic data sampled at 32 Hz. Once the baseline is acquired, the experimental compounds are dosed in a cumulative manner in half log unit increments. The contact time for each dose is 10 min with the final 5 min being the period of time that the dose response data are acquired. If 30 μ M of the test compound does not abolish the detrusor mechanical activity, then 30 μ M cromakalim, a putative potassium channel opener, is dosed to establish a maximum response. The effect of the compound at each dose is expressed as % of the maximum inhibitory response, which is further normalized with respect to the corresponding effect of the compound vehicle control. The normalized response is then used to derive the IC_{50} of the relaxant activity of the compound through the application of Marquardt's nonlinear iterative curve fitting technique to a standard dose-response function.

The ability of compounds according to the invention to open potassium channels in detrusor smooth muscle can be further demonstrated by a second in vitro test.

This second in vitro test is similar to the one described above with regard to tissue preparation and data acquisition. However, the following exceptions are noted. In this second test, the contraction of the detrusor strips during priming and after the equilibration period is achieved with 80 mM instead of 15 mM KCl

(total concentration in the bath). A sustained tension in the tissue is evident after this high KCl stimulation, because voltage-sensitive calcium channels have been rendered open to permit an influx of calcium into the cells and the development of tonic tension. This tension is totally abolished with 300 μ M of papaverine, which is thereby used to establish the maximum response in this test.

Typical calcium channel blockers like nifedipine, nimodipine, isradipine, and verapamil are able to relax and reduce the myogenic activity of guinea pig detrusor strips in both tests by virtue of their blocking action on calcium channels. However, all of the aforementioned calcium channel blockers are more potent in the second test when 80 mM KCl is used, than in the first test where 15 mM KCl is used. In contrast, while the putative potassium channel opener cromakalim has a potent relaxant activity in the first test with an IC_{50} in the range of 0.6 to 0.9 μ M, it demonstrates insignificant relaxant activity in the second test at concentrations as high as 30 μ M. Thus, the profile of a higher relaxant activity in the first test than in the second of compounds according to the invention indicates that the compounds are functioning as potassium channel openers.

The ability of the compounds according to the invention to act as potassium channel openers on bladder tissue may be further demonstrated by a standard test which measures the effect of test compounds on the rate of efflux of rubidium from the tissue.

For example, the compound 3-chloro-4-cyanophenyl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide has been found to give an IC_{50} of 3.8 in the above test. Other compounds of formula I which have been tested and found to give an IC_{50} of 30 μ M or less include those indicated in the Table below.

TABLE

Example	R ¹	R ²	R ³	R ⁴	A-B
1	NO ₂	H	CF ₃	CH ₃	NHCO
2	CH ₃ SO ₂	Cl	"	"	"
3.	Cl	(C ₂ H ₅)CH ₃ CONH	"	"	"
4.	NO ²	phenylthio	"	"	"
5.	"	CF ₃	"	"	"
6.	CN	CN	"	"	"
7.	Br	CF ₃	"	"	"
8.	NO ²	"	"	"	"
9.	NO ₂	H	"	"	OCH ₂
10.	CN	H	"	"	NHCO
11.	cyclohexylSO ₂	H	"	"	"
12.	Cl	Cl	"	"	"
13.	(C ₂ H ₅)CH ₃ CONH	H	"	"	"
14.	BzSO ₂	H	"	"	"
15.	NO ₂	CF ₃	CF ₂ H	CH ₃	"
16.	CN	"	"	"	"
17.	H	CN	CF ₃	CH ₃	"
18.	NO ₂	CF ₃	"	C ₂ H ₅	"
19.	CN	"	"	CH ₃	"
20.	Cl	NO ₂	"	"	"

Bz = benzyl

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

Example 1.

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I (hereafter referred to as "compound X"), for therapeutic or prophylactic use in humans:

(a) Tablet

	<u>mg/tablet</u>
Compound X.....	50.0
Mannitol, USP.....	223.75
Croscarmellose sodium.....	6.0
Maize starch.....	15.0
Hydroxypropylmethylcellulose (HPMC), USP.....	2.25
Magnesium stearate.....	3.0

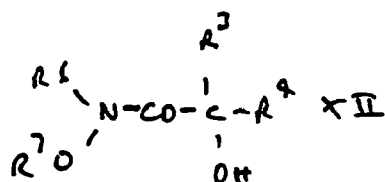
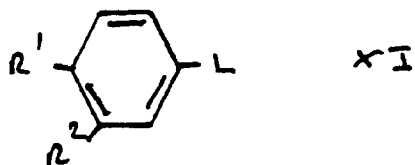
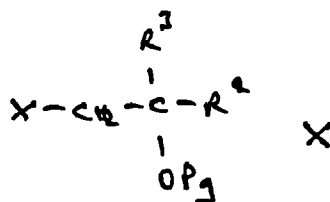
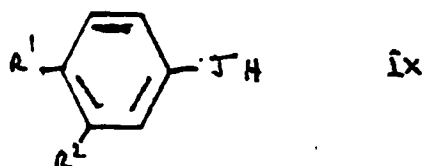
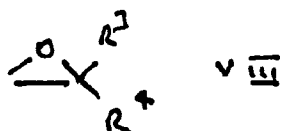
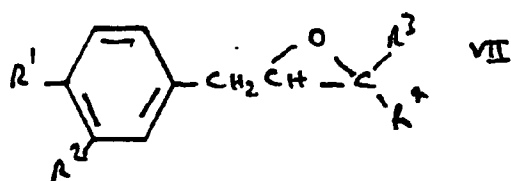
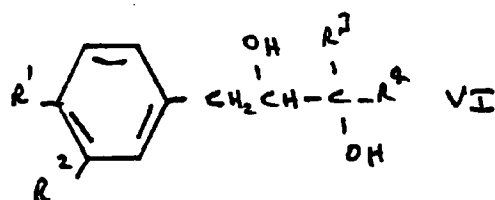
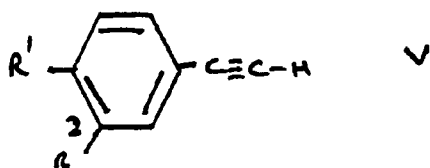
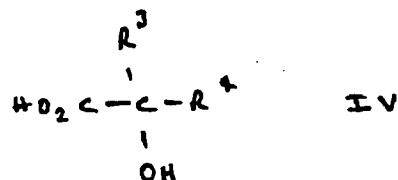
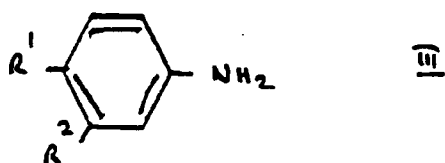
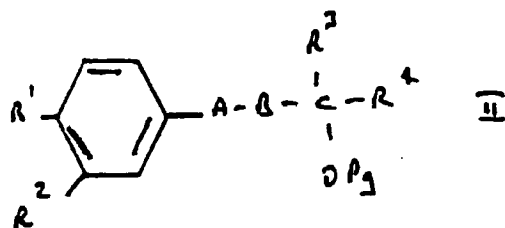
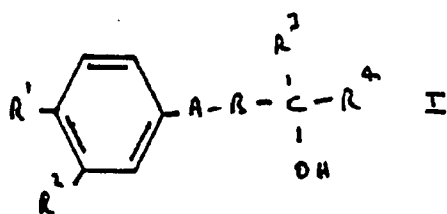
(b) Capsule

Compound X.....	10.0
Mannitol, USP.....	488.5
Croscarmellose sodium.....	15.0
Magnesium stearate.....	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

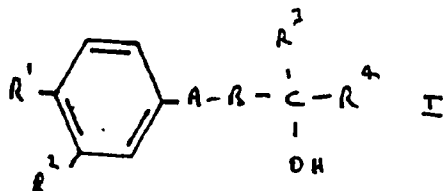
OP09323 11MAY93

MAH/MEB

CHEMICAL FORMULAE

Claims.

1. The use of a compound of formula I



wherein:

one of R^1 and R^2 represents (1-4C)alkyl, {(1-4C)alkyl}{(1-4C)alkanoyl}amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R^1 and R^2 represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, provided that when R^1 is cyano, R^2 is not phenylthio;

A-B is selected from NHCO , OCH_2 , NHCH_2 , trans-vinylene and ethynylene;

R^3 and R^4 are independently (1-3C)alkyl substituted by from 0 to $2k+1$ atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said (1-3C)alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4 , together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to $2m-2$ fluorine atoms wherein m is the number of carbon atoms in said ring;

or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I;

or a pharmaceutically acceptable salt of said compound or said ester in the manufacture of a medicament for the treatment of urinary incontinence.

2. Use as claimed in claim 1, in which R^1 is hydrogen, methyl, ethylacetyl-amino, methanesulphonyl, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, cyclohexylsulphonyl, phenylthio or benzylsulphonyl.
3. Use as claimed in claim 1, in which R^2 is hydrogen, ethylacetyl-amino, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl or phenylthio.
4. Use as claimed in any one of claims 1 to 3, in which R^1 and R^2 together with the phenyl group to which they are attached are 4-methylphenyl, 4-ethylacetylaminophenyl, 3-chloro-4-methanesulphonylphenyl, 4-nitrophenyl, 3-phenylthio-4-nitrophenyl, 3-chloro-4-nitrophenyl, 3-trifluoromethyl-4-nitrophenyl, 4-cyanophenyl, 3,4-dicyanophenyl, 3-chloro-4-cyanophenyl, 3-trifluoromethyl-4-cyanophenyl, 3-cyanophenyl, 4-chloro-3-ethylacetylaminophenyl, 4-bromo-3-trifluoromethylphenyl, 4-cyclohexylsulphonylphenyl, 3,4-dichlorophenyl or 4-benzylsulphonylphenyl.
5. Use as claimed in any one of claims 1 to 4, in which A-B represents NHCO , OCH_2 , trans-vinylene or ethynylene.
6. Use as claimed in claim 5, in which A-B represents NHCO , trans-vinylene or ethynylene.
7. Use as claimed in any one of claims 1 to 6, in which either R^3 and R^4 both represent difluoromethyl, or R^4 represents trifluoromethyl and R^3 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl.
8. Use as claimed in claim 7, in which R^4 represents trifluoromethyl and R^3 represents methyl.
9. Use as claimed in any one of claims 1 to 8, in which the compound of formula I is in the form of the (S)-enantiomer.

-19-

Relevant Technical Fields (i) UK Cl (Ed.M) A5B (BHA; BJA) (ii) Int Cl (Ed.5) A61K (31/085, 31/165, 31/135, 31/275)	Search Examiner Dr C L DAVIES
	Date of completion of Search 18 AUGUST 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ON-LINE DATABASES - CAS-ONLINE	Documents considered relevant following a search in respect of Claims :- 1 TO 9

Categories of documents

- | | |
|---|--|
| X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art. | P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document. |
|---|--|

Category	Identity of document and relevant passages	Relevant to claim(s)
A	GB 2102287 A (SCHERING AG) see Example IV page 4	

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).



①9 BUNDESREPUBLIK

DEUTSCHLAND



DEUTSCHES

PATENTAMT

⑫ Offenlegungsschrift

⑩ DE 42 17 928 A 1

⑳ Aktenzeichen: P 42 17 928.9

㉑ Anmeldetag: 30. 5. 92

㉒ Offenlegungstag: 2. 12. 93

㉓ Int. Cl. 5:

C 07 C 69/712

C 07 C 59/135

C 07 C 205/37

A 01 N 25/32

A 01 N 47/36

A 01 N 43/50

A 01 N 43/40

C 07 D 213/60

C 07 D 237/10

C 07 D 405/12

C 07 D 413/12

C 07 D 417/12

DE 42 17 928 A 1

// A01N 39/02,43/60,43/74,37/22,37/26,43/82,43/56,47/12,37/50,35/10,43/90 (C07D 213/60,269:02,283:02,317:32)
(C07D 237/10,269:02,283:02,317:32)

㉔ Anmelder:

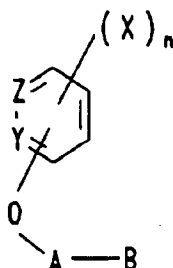
Hoechst AG, 65929 Frankfurt, DE

㉕ Erfinder:

Ziemer, Frank, Dr., 6239 Kriftel, DE; Willms, Lothar, Dr., 5416 Hillscheid, DE; Bauer, Klaus, Dr., 6450 Hanau, DE; Bieringer, Hermann, Dr., 6239 Eppstein, DE

㉖ Neue Mischungen aus Herbiziden und Antidots, neue (Hetero-) Aryloxy-Verbindungen, Verfahren zu deren Herstellung, diese enthaltenden Mittel und deren Verwendung

㉗ Die Erfindung betrifft Pflanzenschutzmittel mit einer Herbizid-Safener-Wirkstoffkombination. Die Herbizide sind aus der Gruppe der ALS-Hemmstoffe (ALS = Acetolacetatsynthase) wie Sulfonylharnstoffe, Imidazoline, Triazolopyrimidin-Sulfonamide, Pyrimidylxypyridincarbonsäurederivate und Pyrimidylxylbenzoesäurederivate. Die Safener sind Verbindungen der Formel I



die wie in Anspruch 1 definiert ist, wobei
Z, Y = N oder CH, wobei H durch X ersetzt sein kann,
X = H, Hal, Haloalkyl oder -alkoxy, Alkyl, Alkoxy, Alkylthio,
NO₂, NH₂, CN, Alkylsulfonyl,
A = Alkylen oder Alkenylen,
B = Carboxy oder ein Derivat der Carboxygruppe
bedeuten.

Die Mischungen eignen sich vor allem zum Bekämpfen von
Schadpflanzen in den Nutzpflanzenkulturen Mais und Ge-
treide.

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

BUNDESDRUCKEREI 10. 93 308 048/365

28/67

DE 42 17 928 A 1

Beschreibung

Neue Mischungen aus Herbiziden und Antidots, neue (Hetero-)Aryloxy-Verbindungen, Verfahren zu deren Herstellung, diese enthaltende Mittel und deren Verwendung.

Die Erfindung betrifft das technische Gebiet der Pflanzenschutzmittel, insbesondere Wirkstoff-Antidot-Kombinationen, die hervorragend für den Einsatz gegen konkurrierende Schadpflanzen in Nutzpflanzen geeignet sind.

Bei der Anwendung von Pflanzenbehandlungsmitteln, insbesondere bei der Anwendung von Herbiziden, können unerwünschte Schäden an den behandelten Kulturpflanzen auftreten. Die Herbizide sind jedoch nicht voll verträglich (selektiv) mit einigen wichtigen Kulturpflanzen, wie Mais oder Getreide, so daß ihrem Einsatz enge Grenzen gesetzt sind. Sie können deshalb manchmal überhaupt nicht oder nur in solch geringen Aufwandsmengen eingesetzt werden, daß die erwünschte breite herbizide Wirksamkeit nicht gewährleistet ist. So können beispielsweise viele Herbizide der weiter unten genannten Stoffklassen (A) nicht selektiv in Mais oder in Getreide eingesetzt werden. Besonders bei der Nachauflaufapplikation von Herbiziden ist es wünschenswert, eine derartige Phytotoxizität zu verringern.

Aus EP-A-31 938 ist die Verwendung von Aryloxy-carbonsäurenitrilen und -amidoximen als Safener für Phenoxyphenoxycarbonsäureester, Chloracetanilide und Dimedon-derivate bekannt, EP-A-170 906 beschreibt unter anderem auch Phenoxy-carbonsäureoximester und EP-A-1 54 153 beschreibt Aryloxy-Verbindungen als Safener für Phenoxyphenoxy- sowie Heteroaryloxyphenoxy-herbizide.

In EP-A-1 12 799 werden 4-Chlorphenoxy- sowie 4-Chlor-2-methylphenoxyessigsäure als Safener für 4-(3',5'-Dichlorpyridyl-2'-oxy)-phenoxypropionsäurepropargylester genannt. EP-A-293 062 beschreibt die Verwendung von Aryloxy-Verbindungen als Safener für Cyclohexandion-herbizide und EP-A-88 066 schließlich die Verwendung von 3,5-Bis-(trifluormethyl)-phenoxy-carbonsäurederivaten als Safener insbesondere für Acetamide – speziell Triallate.

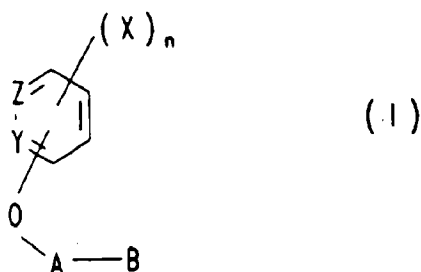
Keines der erwähnten Dokumente gibt einen Hinweis auf eine mögliche Safenerwirkung von Aryloxy-Verbindungen speziell auf Acetolactatsynthase-(ALS)-Hemmstoffe.

Ganz unerwartet haben neue experimentelle Arbeiten gezeigt, daß Aryloxy-, sowie Heteroaryloxy-Verbindungen hervorragend dazu geeignet sind, die phytotoxischen Nebenwirkungen der als ALS-Hemmstoffe wirkenden herbiziden Wirkstoffe (wie Sulfonylharnstoffe, Imidazolinone, Triazolopyrimidin-sulfonamide, Pyrimidylloxypyridincarbonsäure-Derivate und Pyrimidylloxy-benzoesäure-Derivate; siehe beispielsweise EP-A-223 406, EP-A-249 707, EP-A-249 708, EP-A-287 072, EP-A-287 079, EP-A-321 846, EP-A-335 409, EP-A-363 040, EP-A-426 476, EP-A-435 186, WO 91/13065) an Kulturpflanzen, wie Mais und Getreide deutlich zu vermindern oder ganz aufzuheben.

Die vorliegende Erfindung betrifft daher herbizide Mittel, enthaltend

A) mindestens einen herbiziden Wirkstoff aus der Gruppe der Sulfonylharnstoffe, Imidazolinone, Triazolopyrimidin-sulfonamide, Pyrimidylloxy-pyridincarbonsäure-Derivate und Pyrimidylloxy-benzoesäure-Derivate

B) mindestens eine Verbindung der Formel I



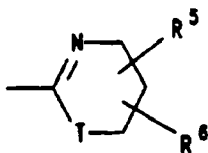
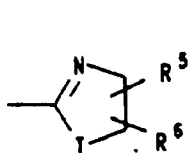
in welcher

Y und Z gleich oder verschieden sind und unabhängig voneinander CX oder N bedeuten;

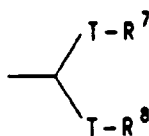
A (C₁–C₆)-Alkandiyl oder (C₃–C₈)-Alkendiyl bedeutet,

B einen Rest der Formel

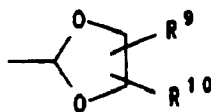
–COOR–, –COSR–, –CONRR⁴,



5



oder



10

15

bedeutet;

X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halogen-(C₁-C₈)-alkyl, Halogen-(C₁-C₈)-alkoxy, (C₁-C₈)-Alkyl, (C₁-C₈)-Alkoxy, Nitro, Amino, Cyano, (C₁-C₈)-Alkylthio oder (C₁-C₈)-Alkylsulfonyl, vorzugsweise Wasserstoff, Halogen, (C₁-C₆)-Halogenalkyl, wie Trifluormethyl, (C₁-C₆)-Halogenalkoxy, wie Difluormethoxy, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkylthio, (C₁-C₆)-Alkylsulfonyl, Nitro, Amino oder Cyano bedeuten;

20

n 3 ist;

25

R Wasserstoff, (C₁-C₁₈)-Alkyl, (C₃-C₁₂)-Cycloalkyl, (C₂-C₁₈)-Alkenyl, (C₂-C₈)-Alkynyl oder -N=CR²R³ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere, vorzugsweise bis zu drei gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen-(C₁-C₈)-alkoxy, Nitro, Cyano, Hydroxy, (C₁-C₈)-Alkoxy, worin eine oder mehrere, vorzugsweise bis zu drei CH₂-Gruppen durch Sauerstoff ersetzt sein können, (C₁-C₈)-Alkylthio, (C₁-C₆)-Alkylsulfonyl, (C₁-C₆)-Alkylsulfonyl, (C₂-C₈)-Alkenylthio, (C₂-C₈)-Alkynylthio, (C₂-C₈)-Alkenyloxy, (C₂-C₈)-Alkynyloxy, (C₃-C₇)-Cycloalkyl, (C₃-C₇)-Cycloalkoxy, Mono- und Di-(C₁-C₄)-alkylamino, (C₁-C₈)-Alkoxy-carbonyl, (C₂-C₈)-Alkenyloxycarbonyl, (C₂-C₈)-Alkynyloxycarbonyl, (C₁-C₈)-Alkylthiocarbonyl, (C₁-C₈)-Alkylcarbonyl, (C₂-C₈)-Alkenylcarbonyl, (C₂-C₈)-Alkynylcarbonyl, 1-(Hydroxyimino)-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkylimino-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkoxyimino-(C₁-C₆)-alkyl, (C₁-C₈)-Alkylcarbonylamino, (C₂-C₈)-Alkenylcarbonylamino, (C₂-C₈)-Alkynylcarbonylamino, Carbamoyl, (C₁-C₈)-Alkylcarbamoyl, Di-(C₁-C₆)-Alkylcarbamoyl, (C₂-C₆)-Alkenylcarbamoyl, (C₂-C₆)-Alkynylcarbamoyl, (C₁-C₈)-Alkoxy-carbonylamino, (C₁-C₈)-Alkyl-amino-carbonylamino, (C₁-C₈)-Alkoxy-carbonyloxy, (C₁-C₈)-Alkylcarbonyloxy, das unsubstituiert oder durch Halogen, Nitro, (C₁-C₄)-Alkoxy und/oder gegebenenfalls substituiertes Phenyl vorzugsweise bis zu dreifach substituiert ist, (C₂-C₆)-Alkenyl-carbonyloxy, (C₂-C₆)-Alkynylcarbonyloxy, Phenyl, Phenyl-(C₁-C₆)-alkoxy, Phenyl-(C₁-C₆)-alkoxy-carbonyl, Phenoxy, Phenoxy-(C₁-C₆)-alkoxy, Phenoxy-carbonyl, Phenoxy-(C₁-C₆)-alkoxy-carbonyl, Phenyl-carbonyloxy, Phenylcarbonylamino, Phenyl-(C₁-C₆)-alkylcarbonylamino, wobei die letztgenannten 10 Reste im Phenylring unsubstituiert oder ein- oder mehrfach, vorzugsweise bis zu dreifach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁-C₄)-Alkyl, (C₁-C₄)-Alkoxy, (C₁-C₄)-Halogenalkyl, (C₁-C₄)-Halogenalkoxy und Nitro substituiert sind, -SiR²R³R⁴, -O-SiR²R³R⁴, R²R³R⁴Si-(C₁-C₆)-alkoxy, -CO-O-NR²R³, -O-N=CR²R³, -N=CR²R³, O-(CH₂)_m-CH(OR²)OR³, R'O-CHR''-CH(OR')-(C₁-C₆)-alkoxy und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls vorzugsweise bis zu dreifach durch Halogen und/oder (C₁-C₄)-Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

30

35

40

45

50

R¹ unabhängig voneinander (C₁-C₄)-Alkyl, oder paarweise zusammen einen (C₁-C₆)-Alkandiylrest und R'' Wasserstoff oder (C₁-C₄)-Alkyl bedeuten;

R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C₁-C₆)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C₂-C₆)-Alkandiylkette stehen;

55

R⁴ Wasserstoff oder gegebenenfalls substituiertes (C₁-C₄)-Alkyl bedeutet; oder

R und R⁴ gemeinsam für eine Alkandiylkette mit 2 bis 5 C-Atomen steht, in der eine CH₂-Gruppe gegebenenfalls durch O, NH oder N(C₁-C₄)-Alkyl ersetzt sein kann;

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff

60

oder (C₁-C₆)-Alkyl bedeuten;

R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁-C₆)-Alkyl, das durch Halogen, (C₁-C₄)-Alkoxy oder Phenyl substituiert sein kann, bedeuten;

R⁹ und R¹⁰ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁-C₆)-Alkyl, das durch Halogen, (C₁-C₄)-Alkoxy oder OH substituiert sein kann, bedeuten;

65

T unabhängig voneinander Sauerstoff oder Schwefel bedeuten; und

m eine ganze Zahl von 0 bis 6 bedeutet;

oder deren Salz.

In den obengenannten Verbindungen der Formel I und im folgenden sind, sofern im einzelnen nicht anders festgelegt, Alkyl, Alkenyl und Alkinyl geradkettig oder verzweigt; entsprechendes gilt für die substituierten Alkyl-, Alkenyl- und Alkinylreste wie Haloalkyl, Hydroxyalkyl, Alkoxyalkyl etc. Alkyl bedeutet z. B. Methyl, Ethyl, n- und i-Propyl, n-, i-, t- und 2-Butyl, Pentyl, Hexyl, wie n-Hexyl, i-Hexyl und 1,3-Dimethylbutyl, Heptyl, wie n-Heptyl, 1-Methylhexyl und 1,4-Dimethylpentyl; Alkenyl bedeutet z. B. Allyl, 1-Methylprop-2-en-1-yl, 2-Methyl-prop-2-en-1-yl, But-2-en-1-yl, But-3-en-1-yl, 1-Methyl-but-3-en und 1-Methyl-but-2-en; Alkinyl bedeutet z. B. Propargyl, But-2-in-1-yl, But-3-in-1-yl, 1-Methyl-but-3-ynyl. Unter substituiertem Alkyl versteht man ein- oder mehrfach, vorzugsweise bis zu dreifach, insbesondere einfach durch gleiche oder verschiedene Reste aus der Reihe Halogen, Hydroxy und (C₁–C₆)-Alkoxy substituiertes Alkyl.

Halogen bedeutet Fluor, Chlor, Brom oder Iod, vorzugsweise Fluor, Chlor oder Brom, insbesondere Fluor oder Chlor. Haloalkyl, -alkenyl und -alkinyl bedeuten durch Halogen teilweise oder vollständig substituiertes Alkyl, Alkenyl bzw. Alkinyl, z. B. CF₃, CHF₂, CH₂F, CF₃CF₂, CH₂FCHCl, CCl₃, CHCl₂, CH₂CH₂Cl; Haloalkoxy ist z. B. OCF₃, OCHF₂, OCH₂F, CF₃CF₂O, OCH₂CF₃.

Gegebenenfalls substituiertes Phenyl ist z. B. Phenyl, das unsubstituiert oder ein- oder mehrfach, vorzugsweise bis zu dreifach durch gleiche oder verschiedene Reste aus der Gruppe Halogen, (C₁–C₄)-Alkyl, (C₁–C₄)-Alkoxy, (C₁–C₄)-Halogenalkyl, (C₁–C₄)-Halogenalkoxy und Nitro substituiert ist, z. B. o-, m- und p-Tolyl, Dimethylphenyl, 2-, 3- und 4-Chlorphenyl, 2-, 3- und 4-Trifluor- und -Trichlorphenyl, 2,4-, 3,5-, 2,5- und 2,3-Dichlorphenyl, o-, m- und p-Methoxyphenyl.

Ein drei- bis siebengliedriger wie oben beschriebener heterocyclischer Rest ist vorzugsweise von Benzol abgeleitet, wovon mindestens ein CH durch N und/oder mindestens zwei benachbarte CH-Paare durch NH, S und/oder O ersetzt sind. Der Rest kann benzokondensiert sein. Er ist gegebenenfalls teilweise oder vollständig hydriert. Es kommen insbesondere Reste wie Oxiranyl, Pyrrolidyl, Piperidyl, Dioxolanyl, Pyrazolyl, Morpholyl, Furyl, Tetrahydrofuryl, Indolyl, Azepinyl, Triazolyl, Thienyl und Oxazolyl in Frage.

Manche Verbindungen der Formel I enthalten ein oder mehrere asymmetrische C-Atome oder Doppelbindungen, die in der allgemeinen Formel I nicht gesondert angegeben sind. Die durch ihre spezifische Raumform definierten möglichen Stereoisomeren, wie Enantiomere, Diastereomere, E- und Z-Isomere sowie deren Gemische sind jedoch alle von der Formel I umfaßt.

Die Verbindungen der Formel I können Salze bilden, bei denen der Rest R durch ein Äquivalent eines für die Landwirtschaft geeigneten Kations ersetzt wird. Diese Salze sind beispielsweise Metall-, insbesondere Alkali- oder Erdalkalisalze, aber auch Ammoniumsalze oder Salze mit organischen Aminen sowie Salze, die als Kationen Sulfonium- oder Phosphoniumionen enthalten.

Als Salzbildner eignen sich besonders Metalle und organische Stickstoffbasen, vor allem quartäre Ammoniumbasen. Hierbei kommen als zur Salzbildung geeignete Metalle Erdalkalimetalle, wie Magnesium oder Calcium, vor allem aber Alkalimetalle in Betracht, wie Lithium und insbesondere Kalium und Natrium.

Beispiele für zur Salzbildung geeignete Stickstoffbasen sind primäre, sekundäre oder tertiäre, aliphatische und aromatische, gegebenenfalls am Kohlenwasserstoffrest hydroxilierte Amine, wie Methylamin, Ethylamin, Propylamin, Isopropylamin, die vier isomeren Butylamine, Dimethylamin, Diethylamin, Dipropylamin, Diisopropylamin, Di-n-Butylamin, Pyrrolidin, Piperidin, Morpholin, Trimethylamin, Triethylamin, Tripropylamin, Chinuclidin, Pyridin, Chinolin, Isochinolin sowie Methanolamin, Ethanolamin, Propanolamin, Dimethanolamin, Diethanolamin oder Triethanolamin.

Beispiele für quartäre Ammoniumbasen sind Tetraalkylammoniumkationen, in denen die Alkylreste unabhängig voneinander geradkettige oder verzweigte (C₁–C₆)-Alkylgruppen sind, wie das Tetramethylammoniumkation, das Tetraethylammoniumkation oder das Trimethylethylammoniumkation, sowie weiterhin das Trimethylbenzylammoniumkation, das Triethylbenzylammoniumkation und das Trimethyl-2-hydroxyethylammoniumkation.

Besonders bevorzugt als Salzbildner sind das Ammoniumkation und Di- sowie Trialkylammoniumkationen, in denen die Alkylreste unabhängig voneinander geradkettige oder verzweigte, gegebenenfalls durch eine Hydroxylgruppe substituierte (C₁–C₆)-Alkylgruppen darstellen, wie beispielsweise das Dimethylammoniumkation, das Trimethylammoniumkation, das Triethylammoniumkation, das Di-(2-hydroxyethyl)-ammoniumkation und das Tri-(2-hydroxyethyl)-ammoniumkation.

Bevorzugt sind solche Mittel, worin in der Verbindung der Formel I

A (C₁–C₄)-Alkandyl oder (C₃–C₆)-Alkendiyl bedeutet,

X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halogen-(C₁–C₆)-alkyl, Halogen-(C₁–C₆)-alkoxy, (C₁–C₈)-Alkyl, (C₁–C₈)-Alkoxy, Nitro, Amino, Cyano, (C₁–C₆)-Alkylthio oder (C₁–C₈)-Alkylsulfonyl, vorzugsweise Wasserstoff, Halogen, (C₁–C₆)-Halogenalkyl, wie Trifluormethyl, (C₁–C₆)-Halogenalkoxy, wie Difluormethoxy, (C₁–C₆)-Alkyl, (C₁–C₆)-Alkoxy, (C₁–C₆)-Alkylthio, (C₁–C₆)-Alkylsulfonyl, Nitro, Amino oder Cyano bedeuten, wobei mindestens ein Rest X für Wasserstoff steht; n 3 ist;

R Wasserstoff, (C₁–C₁₂)-Alkyl, (C₃–C₈)-Cycloalkyl, (C₂–C₁₂)-Alkenyl, (C₂–C₈)-Alkinyl oder –N=CR²R³ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere, vorzugsweise bis zu drei gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen-(C₁–C₈)-alkoxy, Nitro, Cyano, Hydroxy, (C₁–C₈)-Alkoxy, worin eine oder mehrere, vorzugsweise bis zu drei CH₂-Gruppen durch Sauerstoff ersetzt sein können, (C₁–C₈)-Alkylthio, (C₁–C₆)-Alkylsulfonyl, (C₁–C₆)-Alkylsulfonyl, (C₂–C₈)-Alkenylthio, (C₂–C₈)-Alkylthio, (C₂–C₈)-Alkenyloxy, (C₂–C₆)-Alkinyloxy, (C₃–C₇)-Cycloalkyl, (C₃–C₇)-Cycloalkoxy, Mono- und Di-(C₁–C₄)-alkylamino, (C₁–C₈)-Alkoxyalkyl, (C₂–C₈)-Alkenyloxyalkyl, (C₂–C₈)-Alkylthioalkyl, (C₁–C₈)-Alkylalkyl, (C₂–C₈)-Alkenylalkyl, (C₂–C₈)-Alkylalkyl, 1-(Hydroxyimino)-(C₁–C₈)-alkyl, 1-(C₁–C₄)-Alkylimino-(C₁–C₆)-alkyl, 1-(C₁–C₄)-Alkoxyimino-(C₁–C₆)-alkyl, (C₁–C₈)-Alkylalkylalkylamino, (C₂–C₈)-Alkenylalkylalkylamino,

(C₂—C₈)-Alkylcarbonylamino, Carbamoyl, (C₁—C₈)-Alkylcarbamoyl, Di-(C₁—C₆)-Alkylcarbamoyl, (C₂—C₆)-Alkenylcarbamoyl, (C₂—C₆)-Alkylcarbamoyl- (C₁—C₈)-Alkoxy-carbonylamino, (C₁—C₈)-Alkyl-amino-carbonylamino, (C₁—C₈)-Alkoxy-carbonyloxy, (C₁—C₈)-Alkyl-carbonyloxy, das unsubstituiert oder durch Halogen, Nitro, (C₁—C₄)-Alkoxy und/oder gegebenenfalls substituiertes Phenyl vorzugsweise bis zu dreifach substituiert ist, (C₂—C₆)-Alkenyl-carbonyloxy, (C₂—C₆)-Alkyl-carbonyloxy, Phenyl, Phenyl-(C₁—C₆)-alkoxy, Phenyl-(C₁—C₆)-alkoxy-carbonyl, Phenoxy, Phenoxy-(C₁—C₆)-alkoxy, Phenoxy-carbonyl, Phenoxy-(C₁—C₆)-alkoxy-carbonyl, Phenyl-carbonyloxy, Phenyl-carbonylamino, Phenyl-(C₁—C₆)-alkyl-carbonylamino, wobei die letztgenannten 10 Reste im Phenylring unsubstituiert oder ein- oder mehrfach, vorzugsweise bis zu dreifach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁—C₄)-Alkyl, (C₁—C₄)-Alkoxy, (C₁—C₄)-Halogenalkyl, (C₁—C₄)-Halogenalkoxy und Nitro substituiert sind, —SiR²R³R⁴, —O—SiR²R³R⁴, R²R³R⁴Si-(C₁—C₆)-alkoxy, —CO—O—NR²R³, —O—N=CR²R³, —N=CR²R³, O—(CH₂)_mCH(OR²)OR³, R'O—CHR''—CH(OR')(C₁—C₆)-alkoxy und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls vorzugsweise bis zu dreifach durch Halogen und/oder (C₁—C₄)-Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

R' unabhängig voneinander (C₁—C₄)-Alkyl, oder paarweise zusammen einen (C₁—C₆)-Alkandiyrest und R'' Wasserstoff oder (C₁—C₄)-Alkyl bedeuten;

R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C₁—C₆)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C₂—C₆)-Alkandiykette stehen;

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl bedeuten; R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl, das durch Halogen, (C₁—C₄)-Alkoxy oder Phenyl substituiert sein kann, bedeuten;

R⁹ und R¹⁰ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl, das durch Halogen, (C₁—C₄)-Alkoxy oder OH substituiert sein kann, bedeuten;

m eine ganze Zahl von 0 bis 6 bedeutet;

und die übrigen Reste oder Variablen wie oben definiert sind.

Insbesondere bevorzugt sind Mittel, worin in Formel I

A (C₁—C₃)-Alkandiy oder (C₃—C₄)-Alkandiy, wie CH₂, CH(CH₃), CH₂—CH₂, (CH₂)₃ oder C(CH₃)₂ bedeutet;

X wie oben definiert ist und mindestens zwei Reste X für Wasserstoff stehen;

n 3 ist;

R Wasserstoff, (C₁—C₁₂)-Alkyl, (C₃—C₈)-Cycloalkyl, (C₂—C₁₂)-Alkenyl, (C₂—C₈)-Alkyl oder —N=CR²R³ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere, vorzugsweise zwei, insbesondere einen, gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Hydroxy, (C₁—C₈)-Alkoxy, worin eine oder mehrere, vorzugsweise zwei, insbesondere eine CH₂-Gruppe(n) durch Sauerstoff ersetzt sein kann, (C₁—C₄)-Alkylthio, (C₂—C₄)-Alkenylthio, (C₂—C₄)-Alkylthio, (C₂—C₄)-Alkenyloxy, (C₂—C₄)-Alkinyloxy, Mono- und Di-(C₁—C₂)-alkylamino, (C₁—C₄)-Alkoxy-carbonyl, (C₂—C₄)-Alkenyloxy-carbonyl, (C₂—C₄)-Alkinyloxy-carbonyl, (C₁—C₄)-Alkyl-carbonyl, (C₂—C₄)-Alkenyl-carbonyl, (C₂—C₄)-Alkyl-carbonyl, (C₁—C₄)-Alkyl-carbonylamino, (C₂—C₄)-Alkenyl-carbonylamino, Carbamoyl, (C₁—C₈)-Alkylcarbamoyl, Di-(C₁—C₆)-Alkylcarbamoyl, (C₁—C₄)-Alkoxy-carbonyloxy, (C₁—C₄)-Alkyl-carbonyloxy, das unsubstituiert oder vorzugsweise bis zu zweifach durch Halogen und/oder (C₁—C₄)-Alkoxy substituiert ist, (C₂—C₄)-Alkenyl-carbonyloxy, (C₂—C₄)-Alkyl-carbonyloxy, Phenyl, Phenyl-(C₁—C₄)-alkoxy, Phenyl-(C₁—C₄)-alkoxy-carbonyl, Phenoxy, Phenoxy-(C₁—C₄)-alkoxy, Phenoxy-carbonyl, Phenoxy-(C₁—C₄)-alkoxy-carbonyl, Phenyl-carbonyloxy, wobei die letztgenannten 8 Reste im Phenylring unsubstituiert oder durch einen oder mehrere, vorzugsweise zwei gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁—C₂)-Alkyl, (C₁—C₂)-Alkoxy, (C₁—C₂)-Halogenalkyl, (C₁—C₂)-Halogenalkoxy und Nitro substituiert sind, —SiR²R³R⁴, O—SiR²R³R⁴, R²R³R⁴Si-(C₁—C₄)-alkoxy, —O—N=CR²R³, —N=CR²R³, O—(CH₂)_mCH(OR²)OR³, R'O—CHR''—CH(OR')(C₁—C₆)-alkoxy und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls vorzugsweise bis zu dreifach durch Halogen und/oder (C₁—C₄)-Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

R' unabhängig voneinander (C₁—C₄)-Alkyl, oder paarweise zusammen einen (C₁—C₆)-Alkandiyrest und R'' Wasserstoff oder (C₁—C₄)-Alkyl bedeuten;

R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C₁—C₆)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C₂—C₆)-Alkandiykette stehen;

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl bedeuten; R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl, das durch Halogen, (C₁—C₄)-Alkoxy oder Phenyl substituiert sein kann, bedeuten;

R⁹ und R¹⁰ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁—C₆)-Alkyl, das durch Halogen, (C₁—C₄)-Alkoxy oder OH substituiert sein kann, bedeuten;

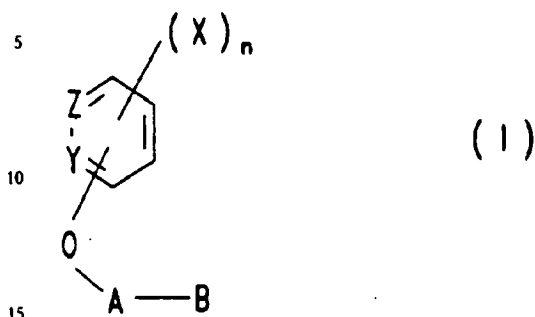
m eine ganze Zahl von 0 bis 2 bedeutet

und die übrigen Reste oder Variablen wie oben definiert sind.

Die Erfindung betrifft auch ein Verfahren zum Schutz von Kulturpflanzen, vorzugsweise Getreide- oder Maispflanzen, vor phytotoxischen Nebenwirkungen von Herbiziden, das dadurch gekennzeichnet ist, daß eine wirksame Menge mindestens einer Verbindung der in Formel I vor, nach oder gleichzeitig mit dem obengenannten herbiziden Wirkstoff auf die Pflanzen, Pflanzensamen oder die Anbaufläche appliziert wird.

Die Erfindung betrifft weiterhin die Verwendung von Verbindungen der Formel I zum Schutz von Kultur-

pflanzen vor phytotoxischen Nebenwirkungen der oben definierten Herbizide.
Die Erfindung betrifft ferner neue Verbindungen der Formel I,



in welcher

Y und Z gleich oder verschieden sind und unabhängig voneinander CX oder N bedeuten;

20 X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halogen-(C₁-C₈)-alkyl, Halogen-(C₁-C₈)-alkoxy, (C₁-C₈)-Alkyl, (C₁-C₈)-Alkoxy, Nitro, Amino, Cyano, (C₁-C₈)-Alkylthio oder (C₁-C₈)-Alkylsulfonyl, vorzugsweise Halogen, (C₁-C₆)-Halogenalkyl, wie Trifluormethyl, (C₁-C₆)-Halogenalkoxy, wie Difluormethoxy, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkoxy, (C₁-C₆)-Alkylthio, (C₁-C₆)-Alkylsulfonyl, Nitro, Amino oder Cyano bedeuten;

n 3 ist;

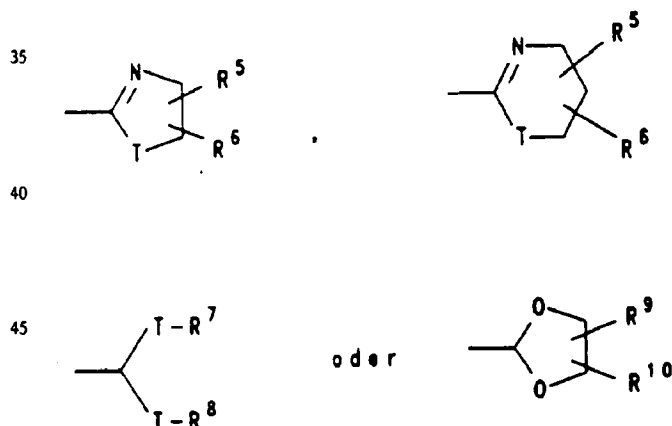
25 R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C₁-C₆)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C₂-C₆)-Alkandiyolkette stehen und

A) für den Fall, daß mindestens einer der Reste Y und Z Stickstoff bedeutet, dann

A (C₁-C₆)-Alkandiyol oder (C₃-C₈)-Alkandiyol bedeutet;

30 B einen Rest der Formel

-COOR, -COSR, -CONRR⁴,



bedeutet;

R ein Äquivalent eines für die Landwirtschaft geeignetes Kations, (C₁-C₁₈)-Alkyl, (C₃-C₁₂)-Cycloalkyl, (C₃-C₁₈)-Alkenyl, (C₃-C₈)-Alkynyl oder -N=CR²R³ bedeutet,

wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen-(C₁-C₈)-alkoxy, Nitro, Cyano, Hydroxy, (C₁-C₈)-Alkoxy, worin eine oder mehrere CH₂-Gruppen durch Sauerstoff ersetzt sein können, (C₁-C₈)-Alkylthio, (C₁-C₆)-Alkylsulfonyl, (C₁-C₆)-Alkylsulfonyl, (C₂-C₈)-Alkenylthio, (C₂-C₈)-Alkynylthio, (C₂-C₈)-Alkenyloxy, (C₂-C₈)-Alkynyloxy, (C₃-C₇)-Cycloalkyl, (C₃-C₇)-Cycloalkoxy, Mono- und Di-(C₁-C₄)-alkylamino, (C₁-C₈)-Alkoxy-carbonyl, (C₂-C₈)-Alkenyloxy-carbonyl, (C₂-C₈)-Alkynyloxy-carbonyl, (C₁-C₈)-Alkylthio-carbonyl, (C₁-C₈)-Alkyl-carbonyl, (C₂-C₈)-Alkenyl-carbonyl, (C₂-C₈)-Alkynyl-carbonyl, 1-(Hydroxyimino)-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkylimino-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkoxyimino-(C₁-C₆)-alkyl, (C₁-C₈)-Alkyl-carbonylamino, (C₂-C₈)-Alkenyl-carbonylamino, (C₂-C₈)-Alkynyl-carbonylamino, Carbamoyl, (C₁-C₈)-Alkyl-carbamoyl, Di-(C₁-C₆)-Alkyl-carbamoyl, (C₂-C₆)-Alkenyl-carbamoyl, (C₂-C₆)-Alkynyl-carbamoyl, (C₁-C₈)-Alkoxy-carbonylamino, (C₁-C₈)-Alkyl-amino-carbonylamino, (C₁-C₈)-Alkoxy-carbonyloxy, (C₁-C₈)-Alkyl-carbonyloxy, das unsubstituiert oder durch Halogen, Nitro, (C₁-C₄)-Alkoxy und/oder gegebenenfalls substituiertes Phenyl substituiert ist, (C₂-C₆)-Alkenyl-carbonyloxy, (C₂-C₆)-Alkynyl-carbonyloxy, Phenyl, Phenyl-(C₁-C₆)-alkoxy, Phenyl-(C₁-C₆)-alkoxy-carbonyl, Phenoxy, Phenoxy-(C₁-C₆)-alkoxy, Phenoxy-(C₁-C₆)-alkoxy-carbonyl, Phenyl-carbonyloxy, Phenyl-carbonylamino, Phenyl-(C₁-C₆)-alkyl-carbonylamino, wo-

bei die letztgenannten 9 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁-C₄)-Alkyl, (C₁-C₄)-Alkoxy, (C₁-C₄)-Halogenalkyl, (C₁-C₄)-Halogenalkoxy und Nitro substituiert sind, -SiR²R³R⁴, -O-SiR²R³R⁴, R²R³R⁴Si-(C₁-C₆)-alkoxy, -CO-O-NR²R³, -O-N=CR²R³, -N=CR²R³ und O-(CH₂)_m-CH(OR²)OR³, R'O-CHR''-CH(OR')-(C₁-C₆)-alkoxy, und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls durch Halogen und/oder (C₁-C₄)-Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N; 5

R' unabhängig voneinander (C₁-C₄)-Alkyl, oder paarweise zusammen einen (C₁-C₆)-Alkdiylrest und R'' Wasserstoff oder (C₁-C₄)-Alkyl bedeuten, 10

R⁴ Wasserstoff, gegebenenfalls substituiertes (C₁-C₄)-Alkyl, oder R und R⁴ gemeinsam für eine Alkandiyldiylkette mit 2 bis 5 C-Atomen steht, in der eine CH₂-Gruppe gegebenenfalls durch O, NH oder N(C₁-C₄)-Alkyl ersetzt sein kann, und 15

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁-C₆)-Alkyl, bedeuten; R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁-C₆)-Alkyl, das durch Halogen, (C₁-C₄)-Alkoxy oder Phenyl substituiert sein kann bedeuten, 20

R⁹ und R¹⁰ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁-C₆)-Alkyl, das durch Halogen, (C₁-C₄)-Alkoxy oder OH substituiert sein kann bedeuten, T unabhängig voneinander Sauerstoff oder Schwefel bedeuten, und m eine ganze Zahl von 0 bis 6 bedeutet; 25

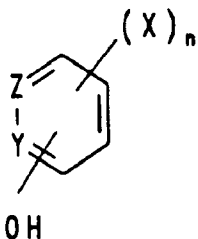
B) oder für den Fall, daß keiner der Reste Y und Z Stickstoff bedeutet, A (C₁-C₆)-Alkandiyldiyl oder (C₄-C₈)-Alkandiyldiyl bedeutet; B ein Rest der Formel -COOR, -COSR oder -CONRR⁴ bedeutet; 30

R (C₃-C₁₈)-Alkyl, (C₃-C₁₂)-Cycloalkyl, (C₂-C₁₈)-Alkenyl oder (C₂-C₈)-Alkinyl bedeutet, wobei jeder der vorstehenden C-haltigen Reste einen oder mehrere gleiche oder verschiedene Reste trägt aus der Gruppe enthaltend (C₂-C₈)-Alkylthio, (C₂-C₈)-Alkylthio, (C₂-C₈)-Alkenyloxy, (C₂-C₈)-Alkinylthio, (C₃-C₇)-Cycloalkyl, (C₃-C₇)-Cycloalkoxy, (C₇-C₁₀)-Alkenyloxycarbonyl, (C₅-C₈)-Alkinylloxycarbonyl, (C₁-C₈)-Alkylthiocarbonyl, (C₂-C₈)-Alkenylcarbonyl, (C₂-C₈)-Alkinylcarbonyl, 1-(Hydroxyimino)-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkylimino-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkoxyimino-(C₁-C₆)-alkyl, (C₁-C₈)-Alkylcarbonylamino, (C₂-C₈)-Alkenylcarbonylamino, (C₂-C₈)-Alkinylcarbonylamino, Carbamoyl, (C₁-C₈)-Alkylcarbamoyl, Di-(C₁-C₆)-Alkylcarbamoyl, (C₂-C₆)-Alkenylcarbamoyl, (C₂-C₆)-Alkinylcarbamoyl, (C₁-C₈)-Alkoxy-carbonylamino, (C₁-C₈)-Alkyl-amino-carbonylamino, (C₁-C₈)-Alkoxy-carbonyloxy, (C₁-C₈)-Alkylcarbonyloxy, das unsubstituiert und/oder durch Halogen, Nitro, (C₁-C₄)-Alkoxy oder gegebenenfalls substituiertes Phenyl substituiert ist, (C₂-C₆)-Alkenylcarbonyloxy, (C₂-C₆)-Alkinylcarbonyloxy, Phenyl-(C₂-C₆)-alkoxy, Phenyl-(C₂-C₆)-alkoxy-carbonyl, Phenoxy-(C₁-C₆)-alkoxy, Phenoxy-(C₂-C₆)-alkoxy-carbonyl, Phenylcarbonyloxy, Phenylcarbonylamino, Phenyl-(C₁-C₆)-alkylcarbonylamino, wobei die letztgenannten 7 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁-C₄)-Alkyl, (C₁-C₄)-Alkoxy, (C₁-C₄)-Halogenalkyl, (C₁-C₄)-Halogenalkoxy und Nitro substituiert sind, -SiR²R³R⁴, -O-SiR²R³R⁴, R²R³R⁴Si-(C₁-C₆)-alkoxy, -CO-O-NR²R³, -O-N=CR²R³, -N=CR²R³ und O-(CH₂)_m-CH(OR²)OR³ und R'O-CHR''-CH(OR')-(C₁-C₆)-alkoxy, R' unabhängig voneinander (C₁-C₄)-Alkyl, oder paarweise zusammen einen (C₁-C₆)-Alkandiyldiylrest und R'' Wasserstoff oder (C₁-C₄)-Alkyl bedeuten; 40

R⁴ Wasserstoff oder gegebenenfalls substituiertes (C₁-C₄)-Alkyl bedeutet; und m eine ganze Zahl von 0 bis 6 bedeutet.

Die Verbindungen der allgemeinen Formel I lassen sich nach allgemein bekannten Verfahren herstellen (Brettell, J. Chem. Soc. 1956, 1891; Eckstein, Roczniki Chem. 30 (1956) 633; US 2 697 708; Newman et al., J. Am. Chem. Soc. 69 (1947) 718; M.P. Cava, N.K. Bhattacharyya, J. Org. Chem. 23 (1958) 1614; D. Heilmann, G. Kempter, Wiss. Z. Pädagog. Hochsch. "Karl Liebknecht", Potsdam 25 (1981) 35; Ger 1 099 544; US 3 010 962).

So kann die Herstellung der erfindungsgemäßen Verbindungen der Formel I in der Weise erfolgen, daß man 1. eine Verbindung der Formel II



worin

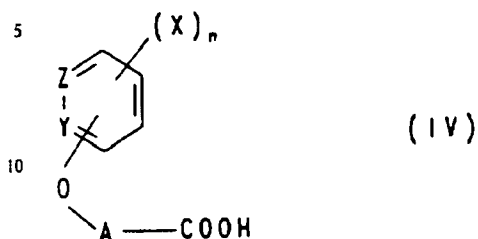
Z, Y, X, n, A und B wie in Formel I definiert sind mit einem Alkancarbonsäurederivat der Formel III,

W-A-B(III),

worin

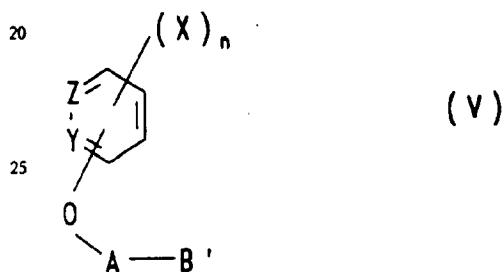
W eine Abgangsgruppe bedeutet, umgesetzt;

2. eine Aryl- oder Heteroaryloxycarbonsäure der Formel IV



15 worin

Z, Y, X, n und A wie in Formel I definiert sind, steht mit Mercaptanen, Aminen oder Alkoholen umgesetzt, oder
3. ein Aryl- oder Heteroaryloxycarbonsäurederivat der Formel V,



30 worin

Z, Y, X, n und A wie bei in Formel I definiert sind und B' eine Alkoxycarbonylgruppe bedeutet, mit Alkoholen oder Aminen umestert bzw. amidiert, und die so erhaltenen Verbindungen der Formel I gegebenenfalls in ihr Salz überführt.

35 Die Umsetzungen nach Variante 1 erfolgen vorzugsweise in dipolar aprotischen Lösungsmitteln wie Dimethylsulfoxid, N,N-Dimethylformamid oder Aceton bei erhöhter Temperatur, insbesondere zwischen 50 und 80°C in Gegenwart einer Base, insbesondere Alkalicarbonaten, wie z. B. Kaliumcarbonat.

Die Umsetzungen nach Variante 2 werden entweder unter Säurekatalyse, wobei vorzugsweise Schwefelsäure Verwendung findet, oder in Gegenwart eines die Carboxylgruppe aktivierenden Reagenzes, wie z. B. Thionylchlorid, Dicyclohexylcarbodiimid oder N,N'-Carbonyldiimidazol in dipolar aprotischen Lösungsmitteln oder Halogenkohlenwasserstoffen, wie z. B. Chloroform oder Tetrachlormethan bei Temperaturen von Raumtemperatur bis zum Siedepunkt des Reaktionsgemisches, insbesondere bei Rückflußtemperatur durchgeführt.

Die Umesterungen bzw. Amidierungen nach Variante 3 erfolgen vornehmlich in der Weise, daß eine Verbindung der Formel V in Gegenwart von Titanalkoholaten als Katalysator mit den Alkoholen bzw. den Aminen bei erhöhten Temperaturen, insbesondere bei Rückflußtemperatur des Reaktionsgemisches umgesetzt wird.

45 Werden die erfindungsgemäßen Verbindungen der Formel I in subtoxischen Konzentrationen zusammen mit den herbiziden Wirkstoffen oder auch in einer beliebigen Reihenfolge ausgebracht, so sind sie in der Lage, die phytotoxischen Nebenwirkungen dieser Herbizide zu reduzieren bzw. völlig aufzuheben, ohne jedoch die Wirksamkeit der Herbizide gegenüber den Schadpflanzen zu vermindern.

50 Geeignete Herbizide, die mit den erfindungsgemäßen Safenern kombiniert werden können, sind beispielsweise:

A) Herbizide vom Typ der Phenoxyphenoxy- und Heteroarylphenoxy-carbonsäure-(C₁-C₄)alkyl-, (C₂-C₄)alkenyl- und (C₃-C₄)alkinylester wie

55 A1) Phenoxy-phenoxy- und Benzyloxy-phenoxy-carbonsäure-derivate, z. B.

2-(4-(2,4-Dichlorphenoxy)-phenoxy)-propionsäuremethylester (Diclofop-methyl),

2-(4-(4-Brom-2-chlorphenoxy)-phenoxy)-propionsäuremethylester (s. DE-A-26 01 548),

2-(4-(4-Brom-2-Fluorphenoxy)-phenoxy)-propionsäuremethylester (s. US-A-4808750),

2-(4-(2-Chlor-4-trifluormethylphenoxy)-phenoxy)-propionsäuremethylester (s. DE-A-24 33 067),

60 2-(4-(2-Fluor-4-trifluormethylphenoxy)-phenoxy)-propionsäuremethylester (s. US-A-4808750),

2-(4-(2,4-Dichlorbenzyl)-phenoxy)propionsäuremethylester (s. DE-A-24 17 487),

4-(4-(4-Trifluormethylphenoxy)-phenoxy)-pent-2-en-säureethylester,

2-(4-(4-Trifluormethylphenoxy)-phenoxy)-propionsäuremethylester (s. DE-A-24 33 067),

A2) "Einkernige" Heteroaryloxy-phenoxy-alkancarbonsäurederivate, z. B.

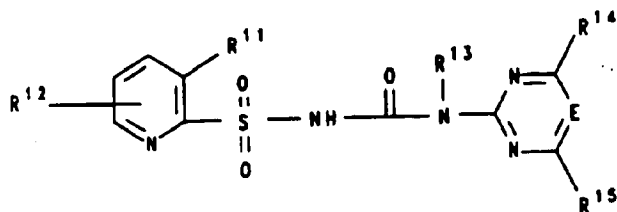
65 2-(4-(3,5-Dichlorpyridyl-2-oxy)-phenoxy)-propionsäureethylester (s. EP-A-2925),

2-(4-(3,5-Dichlorpyridyl-2-oxy)-phenoxy)-propionsäurepropargylester (EP-A-3114),

2-(4-(3-Chlor-5-trifluormethyl-2-pyridyloxy)-phenoxy)-propionsäure-methylester (s. EP-A-3890),

2-(4-(3-Chlor-5-trifluormethyl-2-pyridyloxy)-phenoxy)-propionsäure-ethylester (s. EP-A-3890),

- 2-(4-(5-Chlor-3-fluor-2-pyridyloxy)-phenoxy)-propionsäurepropargylester (EP-A-191736),
 2-(4-(5-Trifluormethyl-2-pyridyloxy)-phenoxy)-propionsäurebutylester (Fusiladebutyl),
 A3) "Zweikernige" Heteroaryloxy-phenoxy-alkancarbonsäurederivate, z. B.
 2-(4-(6-Chlor-2-chinoxalyloxy)-phenoxy)-propionsäuremethylester und -ethylester (Quizalofop-methyl und -ethyl),
 2-(4-(6-Fluor-2-chinoxalyloxy)-phenoxy)-propionsäuremethylester (s. J. Pest. Sci. Vol. 10, 61(1985)),
 2-(4-(6-Chlor-2-chinoxalyloxy)-phenoxy)-propionsäure und -2-isopropylidenaminoxyethylester (Propaquizafop u. Ester),
 2-(4-(6-Chlorbenzoxazol-2-yl-oxy)-phenoxy)-propionsäureethylester (Fenoxapropethyl), dessen D(+) Isomer (Fenoxaprop-P-ethyl) und
 2-(4-(6-Chlorbenzthiazol-2-yloxy)phenoxy)propionsäureethylester (s. DE-A-26 40 730)
 2-(4-(6-Chlorchinoxalyloxy)phenoxy)-propionsäure-tetrahydrofurfur-2-yl-methylester (s. EP-A 323 727).
 B) Herbizide aus der Sulfonylharnstoff-Reihe, wie z. B. Pyrimidin- oder Triazinylaminocarbonyl-[benzol-, pyridin-, pyrazol-, thiophen- und (alkylsulfonyl)alkylamino-]-sulfamide. Bevorzugt als Substituenten am Pyrimidinring oder Triazinring sind Alkoxy, Alkyl, Haloalkoxy, Haloalkyl, Halogen oder Dimethylamino, wobei alle Substituenten unabhängig voneinander kombinierbar sind. Bevorzugte Substituenten im Benzol-, Pyridin-, Pyrazol-, Thiophen- oder (Alkylsulfonyl)alkylamino-Teil sind Alkyl, Alkoxy, Halogen, Nitro, Alkoxy-carbonyl, Aminocarbonyl, Alkylaminocarbonyl, Dialkylaminocarbonyl, Alkoxyaminocarbonyl, Alkyl, Alkoxyaminocarbonyl, Haloalkoxy, Haloalkyl, Alkylcarbonyl, Alkoxyalkyl, (Alkylsulfonyl)alkylamino. Geeignete Sulfonylharnstoff-
 fe sind beispielsweise
 B1) Phenyl- und Benzylsulfonylharnstoffe und verwandte Verbindungen, z. B.
 1-(2-Chlorphenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)harnstoff (Chlorsulfuron),
 1-(2-Ethoxycarbonylphenylsulfonyl)-3-(4-chlor-6-methoxypyrimidin-2-yl)harnstoff (Chlorimuron-ethyl),
 1-(2-Methoxyphenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)harnstoff (Metsulfuron-methyl),
 1-(2-Chlorethoxy-phenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)harnstoff (Triasulfuron),
 1-(2-Methoxycarbonyl-phenylsulfonyl)-3-(4,6-dimethyl-pyrimidin-2-yl)harnstoff Sulfometuron-methyl,
 1-(2-Methoxycarbonylphenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-3-methylharnstoff (Tribenuron-methyl)
 1-(2-Methoxycarbonylbenzylsulfonyl)-3-(4,6-dimethoxy-pyrimidin-2-yl)harnstoff (Bensulfuron-methyl)
 1-(2-Methoxycarbonylphenylsulfonyl)-3-(4,6-bis-(difluormethoxy)pyrimidin-2-yl)harnstoff (Primisulfuron-methyl),
 3-(4-Ethyl-6-methoxy-1,3,5-triazin-2-yl)-1-(2,3-dihydro-1,1-dioxo-2-methylbenzo[b]thiophen-7-sulfonyl)-harnstoff (s. EP-A-79683), 3-(4-Ethoxy-6-ethyl-1,3,5-triazin-2-yl)-1-(2,3-dihydro-1,1-dioxo-2-methylbenzo[b]thiophen-7-sulfonyl)-harnstoff (s. EP-A-79683),
 B2) Thienylsulfonylharnstoffe, z. B.
 1-(2-Methoxycarbonylthiophen-3-yl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)harnstoff (Thifensulfuron-methyl),
 B3) Pyrazolylsulfonylharnstoffe, z. B.
 1-(4-Ethoxycarbonyl-1-methylpyrazol-5-yl-sulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl)harnstoff (Pyrazosulfuron-methyl),
 Methyl-3-chlor-5-(4,6-dimethoxypyrimidin-2-yl-carbamoylsulfamoyl)-1-methyl-pyrazol-4-carboxylat (s. EP 282613),
 B4) Sulfondiamid-Derivate, z. B.
 3-(4,6-Dimethoxypyrimidin-2-yl)-1-(N-methyl-N-methylsulfonylaminosulfonyl)harnstoff (Amidosulfuron) und Strukturanaloge (s. EP-A-0131258 und Z. Pfl. Krankh. Pfl. Schutz, Sonderheft XII, 489—497 (1990)),
 B5) Pyridylsulfonylharnstoffe, z. B.
 1-(3-N,N-Dimethylaminocarbonylpyridin-2-yl-sulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl)harnstoff (Nicosulfuron),
 1-(3-Ethylsulfonylpyridin-2-yl-sulfonyl)-3-(4,6-dimethoxy-pyrimidin-2-yl)harnstoff (DPX-E 9636, s. Brighton Crop Prot. Conf. — Weeds — 1989, S. 23 ff.),
 Pyridylsulfonylharnstoffe, wie sie in DE-A-40 00 503 und DE-A-40 30 577 beschrieben sind, vorzugsweise solche der Formel



worin

E CH oder N vorzugsweise CH,

R¹¹ Iod oder NR¹⁶R¹⁷,

R¹² H, Halogen, Cyano, C₁—C₃-Alkyl, C₁—C₃-Alkoxy, C₁—C₃-Haloalkyl, C₁—C₃-Haloalkoxy, C₁—C₃-Alkylthio,

(C₁—C₃-Alkoxy)-C₁—C₃-alkyl, (C₁—C₃-Alkoxy)-carbonyl, Mono- oder Di-(C₁—C₃-alkyl)-amino, C₁—C₃-Alkylsulfinyl oder -sulfonyl, SO₂—NR^aR^b oder CO—NR^aR^b, insbesondere H

R^a, R^b unabhängig voneinander H, C₁—C₃-Alkyl, C₁—C₃-Alkenyl, C₁—C₃-Alkin oder zusammen —(CH₂)_n—, —(CH₂)₅— oder (CH₂)₂—O—(CH₂)₂—,

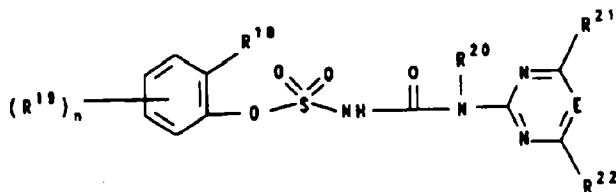
5 R¹³ H oder CH₃,

R¹⁴ Halogen, C₁—C₂-Alkyl, C₁—C₂-Alkoxy, C₁—C₂-Haloalkyl, vorzugsweise CF₃, C₁—C₂-Haloalkoxy, vorzugsweise OCHF₂ oder OCH₂CF₃,

R¹⁵ C₁—C₂-Alkyl, C₁—C₂-Haloalkoxy, vorzugsweise OCHF₂, oder C₁—C₂-Alkoxy, und

10 R¹⁶ C₁—C₄-Alkyl und R¹⁷ C₁—C₄-Alkylsulfonyl oder R¹⁶ und R¹⁷ gemeinsam eine Kette der Formel —(CH₂)₃SO₂— oder —(CH₂)₄SO₂— bedeuten, z. B. 3-(4,6-Dimethoxypyrimidin-2-yl)-1-(3-N-methylsulfonyl-N-methylaminopyridin-2-yl)sulfonylharnstoff, oder deren Salze,

B6) Alkoxyphenoxysulfonylharnstoffe, wie sie in EP-A-03 42 569 beschrieben sind, vorzugsweise solche der Formel



worin

25 E CH oder N, vorzugsweise CH,

R¹⁸ Ethoxy, Propoxy oder Isopropoxy,

R¹⁹ Wasserstoff, Halogen, NO₂, CF₃, CN, C₁—C₄-Alkyl, C₁—C₄-Alkoxy, C₁—C₄-Alkylthio oder (C₁—C₃-Alkoxy)-carbonyl, vorzugsweise in 6-Position am Phenylring,

n 1, 2 oder 3, vorzugsweise 1,

30 R²⁰ Wasserstoff, C₁—C₄-Alkyl oder C₃—C₄-Alkenyl,

R²¹, R²² unabhängig voneinander Halogen, C₁—C₂-Alkyl, C₁—C₂-Alkoxy, C₁—C₂-Haloalkyl, C₁—C₂-Haloalkoxy oder (C₁—C₂-Alkoxy)-C₁—C₂-alkyl, vorzugsweise OCH₃ oder CH₃, bedeuten, z. B. 3-(4,6-Dimethoxypyrimidin-2-yl)-1-(2-ethoxyphenoxy)-sulfonylharnstoff, oder deren Salze, und andere verwandte Sulfonylharnstoffderivate und Mischungen daraus.

35 C) Chloracetanilid-Herbizide wie

N-Methoxymethyl-2,6-diethyl-chloracetanilid (Alachlor),

N-(3'-Methoxyprop-2'-yl)-2-methyl-6-ethyl-chloracetanilid (Metolachlor),

N-(3-Methyl-1,2,4-oxdiazol-5-yl-methyl)-chloroessigsäure-2,6-dimethylanilid, N-(2,6-Dimethylphenyl)-N-(1-pyrazolylmethyl)-chloroessigsäureamid (Metazachlor),

40 D) Thiocarbamate wie

S-Ethyl-N,N-dipropylthiocarbamat (EPTC) oder

S-Ethyl-N,N-diisobutylthiocarbamat (Butylate)

E) Cyclohexandion-Derivate wie

Methyl-3-(1-allyloxyimino)butyl-4-hydroxy-6,6-dimethyl-2-oxocyclohex-3-encarboxylat (Alloxydim)

45 2-(N-Ethoxybutyrimidoyl)-5-(2-ethylthiopropyl)-3-hydroxy-2-cyclohexen-1-on (Sethoxydim),

2-(N-Ethoxybutyrimidoyl)-5-(2-phenylthiopropyl)-3-hydroxy-2-cyclohexen-1-on (Cloproxydim),

2-(1-(3-Chlorallyloxy)iminobutyl)-5-(2-ethylthiopropyl)-3-hydroxy-2-cyclohexen-1-on, 2-(1-(3-Chlorallyloxy)iminopropyl)-5-(2-ethylthiopropyl)-3-hydroxy-cyclohex-2-enon (Clethodim),

2-(1-Allyloxyiminobutyl)-4-methoxycarbonyl-5,5-dimethyl-3-oxocyclohexenol,

50 2-(1-(Ethoxyimino)butyl)-3-hydroxy-5-(thian-3-yl)-cyclohex-2-enon (Cycloxydim), oder

2-(1-Ethoxyiminopropyl)-5-(2,4,6-trimethylphenyl)-3-hydroxy-2-cyclohexen-1-on (Tralkoxydim).

F) 2-(4-Alkyl-5-oxo-2-imidazolin-2-yl)-benzoesäurederivate oder 2-(4-Alkyl-5-oxo-2-imidazolin-2-yl)-heteroaryl-carbonsäurederivate wie z. B.

2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methylbenzoesäuremethylester und

55 2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-4-methylbenzoesäure (Imazamethabenz),

5-Ethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-pyridin-3-carbonsäure (Imazethapyr),

2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-chinolin-3-carbonsäure (Imazaquin),

2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-pyridin-3-carbonsäure (Imazapyr),

5-Methyl-2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-pyridin-3-carbonsäure (Imazethamethapyr)

60 G) Triazolopyrimidinsulfonamidderivate, z. B.

N-(2,6-Difluorphenyl)-7-methyl-1,2,4-triazolo-(1,5-c)-pyrimidin-2-sulfonamid (Flumetsulam),

N-(2,6-Dichlor-3-methylphenyl)-5,7-dimethoxy-1,2,4-triazolo-(1,5-c)-pyrimidin-2-sulfonamid

N-(2,6-Difluorphenyl)-7-fluor-5-methoxy-1,2,4-triazolo-(1,5-c)-pyrimidin-2-sulfonamid

N-(2,6-Dichlor-3-methylphenyl)-7-chlor-5-methoxy-1,2,4-triazolo-(1,5-c)-pyrimidin-2-sulfonamid

65 N-(2-Chlor-6-methoxycarbonyl)-5,7-dimethyl-1,2,4-triazolo-(1,5-c)-pyrimidin-2-sulfonamid

(siehe z. B. EP-A-343 752, US-4 988 812).

Die obengenannten Herbizide der Gruppe A bis G sind dem Fachmann bekannt und in der Regel in "The Pesticide Manual", British Crop Protection Council, 9th Edition (1990—91) oder in "Agricultural Chemicals Book

II-Herbicides", by W.T. Thompson, Thompson Publications, Fresno CA, USA 1990 oder in "Farm Chemicals Handbook '90", Meister Publishing Company, Willoughby OH, USA 1990 beschrieben.

Die herbiziden Wirkstoffe und die erwähnten Safener können zusammen (als fertige Formulierung oder im Tank-mix-Verfahren) oder in beliebiger Reihenfolge nacheinander ausgebracht werden. Das Gewichtsverhältnis Safener : Herbizid kann innerhalb weiter Grenzen variieren und ist vorzugsweise im Bereich von 1 : 10 bis 10 : 1, insbesondere von 1 : 10 bis 5 : 1. Die jeweils optimalen Mengen an Herbizid und Safener sind vom Typ des verwendeten Herbizids oder vom verwendeten Safener sowie von der Art des zu behandelnden Pflanzenbestandes abhängig und lassen sich von Fall zu Fall durch entsprechende Vorversuche ermitteln.

Haupteinsatzgebiete für die Anwendung der Safener sind vor allem Getreidekulturen (Weizen, Roggen, Gerste, Hafer), Reis, Mais, Sorghum, aber auch Baumwolle und Sojabohne, vorzugsweise Getreide und Mais.

Ein besonderer Vorteil der erfindungsgemäßen Safener der Formel I ist bei deren Kombination mit Herbiziden aus der Gruppe der Sulfonylharnstoffen und/oder Imidazolinone festzustellen. Herbizide der genannten Strukturklassen hemmen primär das Schlüsselenzym Acetolactatsynthase (ALS) in den Pflanzen und sind bezüglich des Wirkungsmechanismus daher zumindest partiell verwandt. Einige Herbizide dieser Strukturklassen können speziell in Getreidekulturen und/oder Mais nicht oder nicht genügend selektiv eingesetzt werden. Durch die Kombination mit den erfindungsgemäßen Safenern sind auch bei diesen Herbiziden in Getreide oder Mais hervorragende Selektivitäten zu erreichen.

Die Safener der Formel I können je nach ihren Eigenschaften zur Vorbehandlung des Saatgutes der Kulturpflanze (Beizung der Samen) verwendet werden oder vor der Saat in die Saatsfurchen eingebracht oder zusammen mit dem Herbizid vor oder nach dem Auflaufen der Pflanzen angewendet werden. Voraufaufbehandlung schließt sowohl die Behandlung der Anbaufläche vor der Aussaat als auch die Behandlung der angesäten, aber noch nicht bewachsenen Anbauflächen ein. Bevorzugt ist die gemeinsame Anwendung mit dem Herbizid. Hierzu können Tankmischungen oder Fertigformulierungen eingesetzt werden.

Die benötigten Aufwandmengen der Safener können je nach Indikation und verwendetem Herbizid innerhalb weiter Grenzen schwanken und liegen in der Regel im Bereich von 0,001 bis 5 kg, vorzugsweise 0,005 bis 0,5 kg Wirkstoff je Hektar.

Gegenstand der vorliegenden Erfindung ist deshalb auch ein Verfahren zum Schutz von Kulturpflanzen vor phytotoxischen Nebenwirkungen von Herbiziden, das dadurch gekennzeichnet ist, daß eine wirksame Menge einer Verbindung der Formel vor, nach oder gleichzeitig mit dem Herbizid auf die Pflanzen Pflanzensamen oder die Anbaufläche appliziert wird.

Gegenstand der Erfindung sind auch pflanzenschützende Mittel, die einen Wirkstoff der Formel I und übliche Formulierungshilfsmittel enthalten, sowie herbizide Mittel, die einen Wirkstoff der Formel I und ein Herbizid sowie im Bereich des Pflanzenschutzes übliche Formulierungshilfsmittel enthalten.

Die Verbindungen der Formel I und deren Kombinationen mit einem oder mehreren der genannten Herbizide können auf verschiedene Art formuliert werden, je nachdem welche biologischen und/oder chemisch-physikalischen Parameter vorgegeben sind. Als Formulierungsmöglichkeiten kommen beispielsweise in Frage: Spritzpulver (WP), emulgierbare Konzentrate (EC), wasserlösliche Pulver (SP), wasserlösliche Konzentrate (SL), konzentrierte Emulsionen (EW) wie Öl-in-Wasser und Wasser-in-Öl-Emulsionen, versprühbare Lösungen oder Emulsionen, Kapselsuspensionen (CS) Dispersionen auf Öl- oder Wasserbasis (SC), Suspoemulsionen, Suspensionskonzentrate, Stäubemittel (DP), ölmischbare Lösungen (OL), Beizmittel, Granulate (GR) in Form von Mikro-, Sprüh-, Aufzugs- und Adsorptionsgranulaten, Granulate für die Boden- bzw. Streuapplikation, wasserlösliche Granulate (SG), wasserdispergierbare Granulate (WG), ULV-Formulierungen, Mikrokapseln und Wachse.

Diese einzelnen Formulierungstypen sind im Prinzip bekannt und werden beispielsweise beschrieben in: Winnacker-Küchler, "Chemische Technologie" Band 7, C. Hauser Verlag München, 4. Aufl. 1986; Wade van Valkenburg, "Pesticide Formulations", Marcel Dekker N.Y., 1973; K. Martens, "Spray Drying Handbook", 3rd Ed. 1979, G. Goodwin Ltd. London.

Die notwendigen Formulierungshilfsmittel wie Inertmaterialien, Tenside, Lösungsmittel und weitere Zusatzstoffe sind ebenfalls bekannt und werden beispielsweise beschrieben in: Watkins, "Handbook of Insecticide Dust Diluents and Carriers", 2nd Ed., Darland Books, Caldwell N.J.; H.v.Olphen "Introduction to Clay Colloid Chemistry", 2nd Ed., J. Wiley & Sons, N.Y., Marsden "Solvents Guide", 2nd Ed., Interscience, N.Y. 1963; McCutcheon's "Detergents and Emulsifiers Annual", MC Publ. Corp., Ridgewood N.J.; Sisley and Wood, "Encyclopedia of Surface Active Agents", Chem. Publ. Co. Inc., N.Y. 1964; Schönfeldt, "Grenzflächenaktive Äthylenoxidaddukte", Wiss. Verlagsgesell., Stuttgart 1976; Winnacker-Küchler "Chemische Technologie", Band 7, C. Hauser Verlag München, 4. Aufl. 1986.

Auf der Basis dieser Formulierungen lassen sich auch Kombinationen mit anderen pestizid wirksamen Stoffen, Düngemitteln und/oder Wachstumsregulatoren herstellen, z. B. in Form einer Fertigformulierung oder als Tankmix.

Spritzpulver sind in Wasser gleichmäßig dispergierbare Präparate, die neben dem Wirkstoff außer einem Verdünnungs- oder Inertstoff noch Netzmittel, z. B. polyoxethylierte Alkylphenole, polyoxethylierte Fettalkohole und Fettamine, Fettalkoholpolyglykolethersulfate, Alkylsulfonate oder Alkylarylsulfonate und Dispergiermittel, z. B. ligninsulfonsaures Natrium, 2,2'-dinaphthylmethan-6,6'-disulfonsaures Natrium, dibutyl-naphthalinsulfonsaures Natrium oder auch oleylmethyltaurinsäures Natrium enthalten.

Emulgierbare Konzentrate werden durch Auflösen des Wirkstoffes in einem organischen Lösungsmittel, z. B. Butanol, Cyclohexanon, Dimethylformamid, Xylol oder auch höhersiedenden Aromaten oder Kohlenwasserstoffen unter Zusatz von einem oder mehreren Emulgatoren hergestellt. Als Emulgatoren können beispielsweise verwendet werden: Alkylarylsulfonsäure Calcium-Salze wie Ca-Dodecylbenzolsulfonat oder nichtionische Emulgatoren wie Fettsäurepolyglykolester, Alkylaryl-polyglykolether, Fettalkoholpolyglykolether, Propylenoxid-Ethylenoxid Kondensationsprodukte (z. B. Blockpolymere), Alkylpolyether, Sorbitanfettsäureester, Poly-

oxyethylensorbitanfettsäureester oder Polyoxethylensorbitester.

Stäubemittel erhält man durch Vermahlen des Wirkstoffes mit fein verteilten festen Stoffen, z. B. Talkum, natürlichen Tonen, wie Kaolin, Bentonit und Pyrophyllit, oder Diatomeenerde.

Granulate können entweder durch Verdüsen des Wirkstoffes auf adsorptionsfähiges, granuliertes Inertmaterial hergestellt werden oder durch Aufbringen von Wirkstoffkonzentraten mittels Klebemitteln, z. B. Polyvinylalkohol, polyacrylsaurem Natrium oder auch Mineralölen, auf die Oberfläche von Trägerstoffen wie Sand, Kaoliniten oder von granuliertem Inertmaterial. Auch können geeignete Wirkstoffe in der für die Herstellung von Düngemittelgranulaten üblichen Weise – gewünschtenfalls in Mischung mit Düngemitteln – granuliert werden.

Die agrochemischen Zubereitungen enthalten in der Regel 0,1 bis 99 Gewichtsprozent, insbesondere 0,1 bis 95 Gew.-%, Wirkstoffe der Formel I (Antidot) oder des Antidot/Herbizid-Wirkstoffgemischs und 1 bis 99,9 Gew.-%, insbesondere 5 bis 99,8 Gew.-%, eines festen oder flüssigen Zusatzstoffes und 0 bis 25 Gew.-%, insbesondere 0,1 bis 25 Gew.-%, eines Tensides.

In Spritzpulvern beträgt die Wirkstoffkonzentration z. B. etwa 10 bis 90 Gew.-%, der Rest zu 100 Gew.-% besteht aus üblichen Formulierungsbestandteilen. Bei emulgierbaren Konzentraten beträgt die Wirkstoffkonzentration etwa 1 bis 80 Gew.-% Wirkstoffe. Staubbörmige Formulierungen enthalten etwa 1 bis 20 Gew.-% an Wirkstoffen, versprühbare Lösungen etwa 0,2 bis 20 Gew.-% Wirkstoffe. Bei Granulaten wie wasserdispergierbaren Granulaten hängt der Wirkstoffgehalt zum Teil davon ab, ob die wirksame Verbindung flüssig oder fest vorliegt. In der Regel liegt der Gehalt bei den in Wasser dispergierbaren Granulaten zwischen 10 und 90 Gew.-%.

Daneben enthalten die genannten Wirkstoffformulierungen gegebenenfalls die jeweils üblichen Haft-, Netz-, Dispergier-, Emulgier-, Penetrations-, Lösungsmittel, Füll- oder Trägerstoffe.

Zur Anwendung werden die in handelsüblicher Form vorliegenden Formulierungen gegebenenfalls in üblicher Weise verdünnt, z. B. bei Spritzpulvern, emulgierbaren Konzentraten, Dispersionen und wasserdispergierbaren Granulaten mittels Wasser. Staubbörmige Zubereitungen, Granulate sowie versprühbare Lösungen werden vor der Anwendung üblicherweise nicht mehr mit weiteren inerten Stoffen verdünnt. Mit den äußeren Bedingungen wie Temperatur, Feuchtigkeit, der Art des verwendeten Herbizids u. a. variiert die erforderliche Aufwandmenge der "Antidots".

Folgende Beispiele dienen zur Erläuterung der Erfindung:

A. Formulierungsbeispiele

a) Ein Stäubemittel wird erhalten, indem man 10 Gew.-Teile einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und eine Verbindung der Formel I und 90 Gew.-Teile Talkum als Inertstoff mischt und in einer Schlagmühle zerkleinert.

b) Ein in Wasser leicht dispergierbares, benetzbares Pulver wird erhalten, indem man 25 Gewichtsteile einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und einem Safener der Formel I, 64 Gewichtsteile kaolinhaltigen Quarz als Inertstoff, 10 Gewichtsteile ligninsulfonsaures Kalium und 1 Gew.-Teil oleoilylmethyltaurinsaures Natrium als Netz- und Dispergiermittel mischt und in einer Stößmühle mahlt.

c) Ein in Wasser leicht dispergierbares Dispersionskonzentrat wird erhalten, indem man 20 Gewichtsteile einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und einem Safener der Formel I, 6 Gew.-Teilen Alkylphenolpolyglykolether ([®]Triton X 207), 3 Gew.-Teilen Isotridecanolpolyglykolether (8 EO) und 71 Gew.-Teilen paraffinischem Mineralöl (Siedebereich z. B. ca. 255 bis über 277°C) mischt und in einer Reibkugelmühle auf eine Feinheit von unter 5 Mikron vermahlt.

d) Ein emulgierbares Konzentrat wird erhalten aus 15 Gew.-Teilen einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und einem Safener der Formel I, 75 Gew.-Teilen Cyclohexanon als Lösemittel und 10 Gew.-Teilen oxethyliertes Nonylphenol als Emulgator.

e) Ein in Wasser dispergierbares Granulat wird erhalten, indem man 75 Gew.-Teile einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und einem Safener der Formel I, 10 Gew.-Teile ligninsulfonsaures Calcium, 5 Gew.-Teile Natriumlaurylsulfat, 3 Gew.-Teile Polyvinylalkohol und 7 Gew.-Teile Kaolin

mischt, auf einer Stößmühle mahlt und das Pulver in einem Wirbelbett durch Aufsprühen von Wasser als Granulierflüssigkeit granuliert.

f) Ein in Wasser dispergierbares Granulat wird auch erhalten, indem man 25 Gew.-Teile einer Verbindung der Formel I oder eines Wirkstoffgemischs aus einem Herbizid und einem Safener der Formel I, 5 Gew.-Teile 2,2'-dinaphthylmethan-6,6'-disulfonsaures Natrium, 2 Gew.-Teile oleoilylmethyltaurinsaures Natrium, 1 Gew.-Teil Polyvinylalkohol, 17 Gew.-Teile Calciumcarbonat und 50 Gew.-Teile Wasser

auf einer Kolloidmühle homogenisiert und vorzerkleinert, anschließend auf einer Perlmühle mahlt und die so erhaltene Suspension in einem Sprühturm mittels einer Einstoffdüse zerstäubt und trocknet.

B. Herstellungsbeispiele

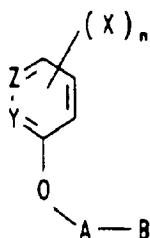
1. 2-Pyridyloxy-essigsäure-(1-methyl)-hexylester (Beispiel 82 aus Tabelle 1)

5.0 g (28 mmol) 2-Pyridyloxy-essigsäure-ethylester wurden in 100 ml 2-Heptanol suspendiert, mit 1 ml Titante-
 traisopropoxid versetzt und 4 h bei 120 °C gerührt. Anschließend wurde das überschüssige 2-Heptanol im
 Ölpumpenvakuum abdestilliert und der Rückstand säulenchromatographisch gereinigt. Man erhielt 6.2 g (90 %
 d. Th.) 2-Pyridyloxy-essigsäure-(1-methyl)-hexylester als farbloses Öl.

2. 2,4-Dichlorphenoxy-essigsäure-ethylester (Beispiel 17 aus Tabelle 1):

15.0 g (68 mmol) 2,4-Dichlorphenoxyessigsäure in 20 ml Ethanol wurden mit 1.3 g (14 mmol) H₂SO₄ versetzt
 und 5 h unter Rückfluß erhitzt. Anschließend wurde im Vakuum eingeeengt der Rückstand auf 100 ml Eiswasser
 gegeben, die organische Phase abgetrennt und die wäßrige Phase ausgeethert. Die vereinigten organischen
 Phasen wurden mit 2n Na₂CO₃-Lösung und Wasser gewaschen, über Magnesiumsulfat getrocknet und einge-
 engt. Man erhielt 8.9 g (53 % d. Th.) 2,4-Dichlorphenoxy-essigsäure-ethylester als farbloses Öl.

In der nachfolgenden Tabelle 1 sind beispielhaft eine Reihe von Verbindungen der folgenden allgemeinen
 Formel I aufgeführt. Falls in der vierten Spalte nicht anders angegeben, bedeutet X jeweils Wasserstoff.



(n = 3)

Tabelle 1

	Bsp.	Y	Z	X	- A - B	Smp.
5						
	1	CX	CX	4-Cl	-CH ₂ -COO-H	
10	2	CX	CX	4-Cl	-CH ₂ -COO-C ₂ H ₅	
	3	CX	CX	4-Cl	-CH ₂ -COO-CH ₂ -CH=CH ₂	
	4	CX	CX	4-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
15	5	CX	CX	4-Cl	-CH ₂ -COO-(CH ₂) ₂ -O-CO-CH ₃	
	6	CX	CX	4-Cl	-CH ₂ -COO-C ₂ H ₅ -O-C ₄ H ₉ (n)	
20	7	CX	CX	4-Cl	-CH ₂ -COO-C ₄ H ₉ (n)	
	8	CX	CX	4-Cl	-CH ₂ -COO-C ₈ H ₁₇ (i)	
	9	CX	CX	4-Cl	-CH ₂ -COONa	
25	10	CX	CX	4-Cl	-CH ₂ -COOK	
	11	CX	CX	4-Cl	-CH ₂ -COONH ₄	
30	12	CX	CX	4-Cl	-CH ₂ -COONH ₂ (CH ₃) ₂	
	13	CX	CX	4-Cl	-CH ₂ -COONH ₃ (C ₇ H ₁₅)	
	14	CX	CX	4-Cl	-CH ₂ -COONH ₂ (C ₂ H ₅ OH) ₂	
35	15	CX	CX	4-Cl	-CH ₂ -COONH(C ₂ H ₅ OH) ₃	
	16	CX	CX	2,4-Di-Cl	-CH ₂ -COO-H	
	17	CX	CX	2,4-Di-Cl	-CH ₂ -COO-C ₂ H ₅	
40	18	CX	CX	2,4-Di-Cl	-CH ₂ -COO-CH ₂ -CH=CH ₂	
	19	CX	CX	2,4-Di-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
45	20	CX	CX	2,4-Di-Cl	-CH ₂ -COO-C ₂ H ₅ -O-C ₄ H ₉ (n)	
	21	CX	CX	2,4-Di-Cl	-CH ₂ -COO-C ₄ H ₉ (n)	
	22	CX	CX	2,4-Di-Cl	-CH ₂ -COO-C ₈ H ₁₇ (i)	
50	23	CX	CX	2,4-Di-Cl	-CH ₂ -COONa	
	24	CX	CX	2,4-Di-Cl	-CH ₂ -COOK	
55	25	CX	CX	2,4-Di-Cl	-CH ₂ -COONH ₄	
	26	CX	CX	2,4-Di-Cl	-CH ₂ -COONH ₂ (CH ₃) ₂	

60

65

Bsp.	Y	Z	X	- A - B	Smp.
27	CX	CX	2,4-Di-Cl	-CH ₂ -COONH ₃ (C ₇ H ₁₅)	
28	CX	CX	2,4-Di-Cl	-CH ₂ -COONH ₂ (C ₂ H ₅ OH) ₂	5
29	CX	CX	2,4-Di-Cl	-CH ₂ -COONH(C ₂ H ₅ OH) ₃	
30	CX	CX	3,4-Di-Cl	-CH ₂ -COO-H	10
31	CX	CX	3,4-Di-Cl	-CH ₂ -COO-C ₂ H ₅	
32	CX	CX	3,4-Di-Cl	-CH ₂ -COO-CH ₂ -CH=CH ₂	
33	CX	CX	3,4-Di-Cl	-CH ₂ -COO-C ₂ H ₅ -O-C ₄ H ₉ (n)	15
34	CX	CX	3,4-Di-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
35	CX	CX	2-CH ₃ , 4-Cl	-CH(CH ₃)-COO-H	20
36	CX	CX	2-CH ₃ , 4-Cl	-CH(CH ₃)-COO-C ₂ H ₅	
37	CX	CX	2-CH ₃ , 4-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
38	CX	CX	2,4-Di-Cl	-(CH ₂) ₃ -COO-H	25
39	CX	CX	2,4-Di-Cl	-(CH ₂) ₃ -COO-C ₂ H ₅	
40	CX	CX	2,4-Di-Cl	-(CH ₂) ₃ -COO-CH(CH ₃)-(CH ₂) ₄ -CH	30
41	CX	CX	4-F	-CH ₂ -COO-H	
42	CX	CX	4-F	-CH ₂ -COO-C ₂ H ₅	
43	CX	CX	4-F	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	35
44	CX	CX	4-F	-CH ₂ -COO-CH ₂ -CH=CH ₂	
45	CX	CX	4-CH ₃	-CH ₂ -COO-C ₂ H ₅	40
46	CX	CX	4-CH ₃	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
47	CX	CX	4-OC ₂ H ₅	-CH ₂ -COO-C ₂ H ₅	45
48	CX	CX	4-OC ₂ H ₅	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
49	CX	CX	2-Cl, 4-CF ₃	-CH ₂ -COO-H	
50	CX	CX	2-Cl, 4-CF ₃	-CH ₂ -COO-C ₂ H ₅	50
51	CX	CX	2-Cl, 4-CF ₃	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
52	CX	CX	4-Br	-CH ₂ -COO-C ₂ H ₅	55
53	CX	CX	4-Br	-CH ₂ -COO-CH ₃	
54	CX	CX	4-Br	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
55	CX	CX	3-Br	-CH ₂ -COO-CH ₃	60
					65

	Bsp.	Y	Z	X	- A - B	Smp.
	56	CX	CX	3-Br	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
5	57	CX	CX	2-F	-CH ₂ -COO-C ₂ H ₅	
	58	CX	CX	2-F	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	59	CX	CX	4-CH(CH ₃) ₂	-CH ₂ -COO-C ₂ H ₅	
10	60	CX	CX	4-CH(CH ₃) ₂	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	61	CX	CX	3-CF ₃	-CH ₂ -COO-C ₂ H ₅	
15	62	CX	CX	3-CF ₃	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	63	CX	CX	4-I	-CH ₂ -COO-C ₂ H ₅	
	64	CX	CX	4-I	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
20	65	CX	CX	3-I	-CH ₂ -COO-C ₂ H ₅	
	66	CX	CX	3-I	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
25	67	CX	CX	4-NO ₂	-CH ₂ -COO-C ₂ H ₅	
	68	CX	CX	4-NO ₂	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	69	N	CX	4,6-Di-Cl	-CH ₂ -COO-C ₂ H ₅	
30	70	N	CX	4,6-Di-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	71	N	CX	4,6-Di-Cl	-CH ₂ -COO-H	
	72	CX	N	2,4-Di-Cl	-CH ₂ -COO-H	
35	73	CX	N	2,4-Di-Cl	-CH ₂ -COO-C ₂ H ₅	
	74	CX	N	2,4-Di-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
40	75	CX	N	2-Cl	-CH ₂ -COO-H	
	76	CX	N	2-Cl	-CH ₂ -COO-C ₂ H ₅	
	77	CX	N	2-Cl	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
45	78	N	CX	4-Cl, 6-F	-CH ₂ -COO-H	
	79	N	CX	4-Cl, 6-F	-CH ₂ -COO-C ₂ H ₅	
50	80	N	CX	4-Cl, 6-F	-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
	81	N	CX		-CH ₂ -COO-C ₂ H ₅	
	82	N	CX		-CH ₂ -COO-CH(CH ₃)-(CH ₂) ₄ -CH ₃	
55	83	CX	CX	4-Cl	-CH ₂ -COO-CH(CH ₃)-CH ₂ -O-CH ₂ -CH=CH ₂	
	84	CX	CX	4-Br	-CH ₂ -COO-CH(CH ₃)-CH ₂ -O-CH ₂ -CH=CH ₂	
60	85	CX	CX	2,4-Di-Cl	-CH ₂ -COO-CH(CH ₃)-CH ₂ -O-CH ₂ -CH=CH ₂	
	86	CX	CX	3,4-Di-Cl	-CH ₂ -COO-CH(CH ₃)-CH ₂ -O-CH ₂ -CH=CH ₂	

Bsp.	Y	Z	X	- A - B	Smp.
87	CX	CX	4-F	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	5
88	CX	CX	4- CF_3	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	
89	CX	CX	3- CF_3	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	10
90	CX	CX	2-Cl, 4- CF_3	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	
91	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{CH}(\text{CH}_3)_2$	
92	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{C}(\text{CH}_3)_3$	15
93	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{CO}-\text{CH}(\text{CH}_3)_3$	
94	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{CO}-\text{CH}_3$	
95	CX	CX	2,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{C}(\text{CH}_3)_3$	20
96	CX	CX	2,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{CH}(\text{CH}_3)_2$	
97	CX	CX	2,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{CO}-\text{C}(\text{CH}_3)_3$	25
98	CX	CX	2,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{CO}-\text{CH}_3$	
99	CX	CX	2- CH_3 , 4-Cl	$-\text{CH}(\text{CH}_3)-\text{COO}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_4-\text{CH}_3$	
100	CX	CX	2- CH_3 , 4-Cl	$-\text{CH}_2-\text{COO}-\text{H}$	30
101	CX	CX	2- CH_3 , 4-Cl	$-\text{CH}_2-\text{COO}-\text{C}_2\text{H}_5$	
102	CX	CX	2- CH_3 , 4-Cl	$-\text{CH}_2-\text{COO}-\text{C}_6\text{H}_{17}(\text{I})$	35
103	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{COCF}_3$	
104	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{COCF}_3$	
105	CX	CX	3,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{COCF}_3$	40
106	CX	CX	3,4-Di-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_3-\text{O}-\text{COCF}_3$	
107	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{NH}-\text{COCH}_3$	
108	CX	CX	4-Cl	$-\text{C}(\text{CH}_3)_2-\text{COO}-\text{C}_2\text{H}_5$	45
109	CX	CX	4-Cl	$-\text{C}(\text{CH}_3)_2-\text{COO}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_4-\text{CH}_3$	
110	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{OC}_2\text{H}_5$	50
111	CX	CX	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}_2-\text{COO}-\text{C}_2\text{H}_5$	
112	N	N	4-Cl	$-\text{CH}_2-\text{COO}-\text{H}$	260°C
113	N	N	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}_3$	93°C 55
114	N	N	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_4-\text{CH}_3$	
115	N	N	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	60
116	N	CX	4-Cl	$-\text{CH}_2-\text{COO}-\text{H}$	130°C
117	N	CX	4-Cl	$-\text{CH}_2-\text{COO}-\text{C}_2\text{H}_5$	33°C
118	N	CX	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_4-\text{CH}_3$	65
119	N	CX	4-Cl	$-\text{CH}_2-\text{COO}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	

C. Biologische Beispiele

Beispiel 1

5 Weizen und Gerste wurden im Gewächshaus in Plastiktöpfen bis zum 3—4 Blattstadium herangezogen und dann nacheinander mit den erfindungsgemäßen Verbindungen und den getesteten Herbiziden im Nachauflaufverfahren behandelt. Die Herbizide und die Verbindungen der Formel I wurden dabei in Form wäßriger Suspensionen bzw. Emulsionen mit einer Wasseraufwandmenge von umgerechnet 300 l/ha ausgebracht. 3—4 Wochen nach der Behandlung wurden die Pflanzen visuell auf jede Art von Schädigung durch die ausgebrachten
 10 Herbizide bonitiert, wobei das Ausmaß der anhaltenden Wachstumshemmung berücksichtigt wurde. Die Bewertung erfolgte in Prozentwerten im Vergleich zu unbehandelten Kontrollen.

Selbst bei starken Überdosierungen des Herbizids werden bei den Kulturpflanzen auftretende schwere Schädigungen deutlich reduziert, geringere Schäden völlig aufgehoben.

15 Mischungen aus Herbiziden und erfindungsgemäßen Verbindungen eignen sich deshalb in ausgezeichneter Weise zur selektiven Unkrautbekämpfung in Getreidekulturen.

Beispiel 2

20 Die Maispflanzen, Unkräuter und Ungräser wurden im Freiland oder im Gewächshaus in Plastiktöpfen bis zum 3—4 Blattstadium herangezogen und nacheinander mit Herbiziden und erfindungsgemäßen Verbindungen der Formel I im Nachauflaufverfahren behandelt. Die Wirkstoffe wurden dabei in Form wäßriger Suspensionen bzw. Emulsionen mit einer Wasseraufwandmenge von umgerechnet 300 l/ha ausgebracht. 4 Wochen nach der Behandlung wurden die Pflanzen visuell auf jede Art von Schädigung durch die ausgebrachten Herbizide bonitiert, wobei insbesondere das Ausmaß der anhaltenden Wachstumshemmung berücksichtigt wurde. Die
 25 Bewertung erfolgte in Prozentwerten im Vergleich zu unbehandelten Kontrollen.

Die Ergebnisse zeigen, daß die erfindungsgemäßen eingesetzten Verbindungen der Formel I starke Herbizidschäden an den Maispflanzen effektiv reduzieren können.

Selbst bei starken Überdosierungen der Herbizide werden bei den Kulturpflanzen auftretende schwere Schädigungen deutlich reduziert und geringere Schäden völlig aufgehoben.

30 Mischungen aus Herbiziden und Verbindungen der Formel I eignen sich deshalb in ausgezeichneter Weise zur selektiven Unkrautbekämpfung in Mais.

Die Ergebnisse der biologischen Versuche sind in der folgenden Tabelle 2 zusammengestellt.

Tabelle 2

Pflanzenschützende Wirkung der erfindungsgemäßen Verbindungen

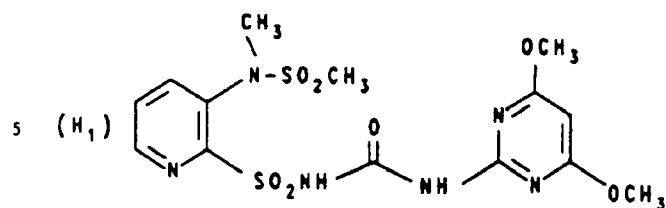
Wirkstoffe	Dosis kg AS/ha	%Schädigung Mais	Echinochloa-Hirse	5
<hr/>				10
H ₁	200	78	-	
	100	75	-	
	50	65	-	15
	25	60	100	
H ₁ + S ₁	200 + 100	35	-	20
	100 + 50	30	-	
	50 + 25	10	-	25
	25 + 12	0	100	
H ₁ + S ₂	200 + 100	50	-	30
	100 + 50	35	-	
	50 + 25	15	-	35
	25 + 12	10	100	
H ₁ + S ₃	200 + 100	45	-	40
	100 + 50	40	-	
	50 + 25	15	-	45
	25 + 12	5	100	
H ₁ + S ₄	200 + 100	35	-	50
	100 + 50	25	-	
	50 + 25	10	-	55
	25 + 12	0	100	

Wuchsstadien: Mais — 4 Blattstadien

Echinochloa — 3 Blattstadien

Gewächshausversuch mit 4 Wiederholungen. Applikation mit 300 ltr. Wasser/ha Bonitur 4 Wochen nach Behandlung.

S₁ (Beispiel 34 aus Tab.1)S₂ (Beispiel 31 aus Tab. 1)S₃ (Beispiel 2 aus Tab.1)S₄ (Beispiel 4 aus Tab. 1)

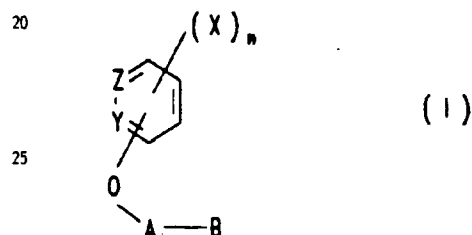


Patentansprüche

1. Herbizides Mittel, enthaltend

A) mindestens einen herbiziden Wirkstoff aus der Gruppe der Sulfonylharnstoffe, Imidazolinon-Triazolopyrimidin-sulfonamide, Pyrimidyloxy-pyridincarbonsäurederivate und Pyrimidyloxy-benzoesäure-derivate in welcher

B) mindestens eine Verbindung der Formel I



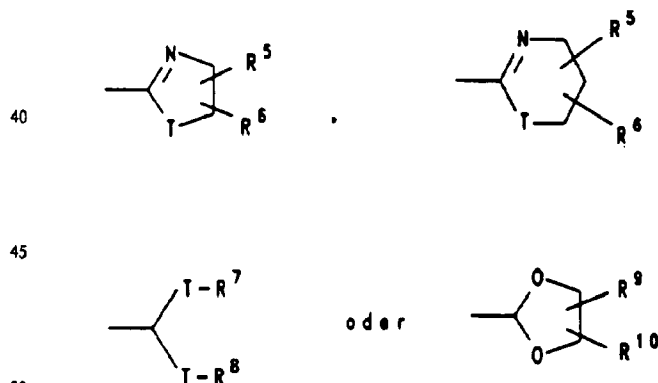
in welcher

Y und Z gleich oder verschieden sind und unabhängig voneinander CX oder N bedeuten;

A (C₁-C₆)-Alkandiyl oder (C₃-C₈)-Alkendiyl bedeutet,

B einen Rest der Formel

-COOR, -COSR, -CONRR⁴,



X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halogen-(C₁-C₈)-alkyl, Halogen-(C₁-C₈)-alkoxy, (C₁-C₈)-Alkyl, (C₁-C₈)-Alkoxy, Nitro, Amino, Cyano, (C₁-C₈)-Alkylthio oder (C₁-C₈)-Alkylsulfonyl bedeuten;

n 3 ist;

R Wasserstoff, (C₁-C₁₈)-Alkyl, (C₃-C₁₂)-Cycloalkyl, (C₂-C₁₈)-Alkenyl, (C₂-C₈)-Alkynyl oder -N=CR²R³ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen-(C₁-C₈)-alkoxy, Nitro, Cyano, Hydroxy, (C₁-C₈)-Alkoxy, worin eine oder mehrere CH₂-Gruppen durch Sauerstoff ersetzt sein können, (C₁-C₈)-Alkylthio, (C₁-C₆)-Alkylsulfinyl, (C₁-C₆)-Alkylsulfonyl, (C₂-C₈)-Alkenylthio, (C₂-C₈)-Alkynylthio, (C₂-C₈)-Alkenyloxy, (C₂-C₈)-Alkynyloxy, (C₃-C₇)-Cycloalkyl, (C₃-C₇)-Cycloalkoxy, Mono- und Di-(C₁-C₄)-alkylamino, (C₁-C₈)-Alkoxy-carbonyl, (C₂-C₈)-Alkenyloxy-carbonyl, (C₂-C₈)-Alkynyloxy-carbonyl, (C₁-C₈)-Alkylthio-carbonyl, (C₁-C₈)-Alkyl-carbonyl, (C₂-C₈)-Alkenyl-carbonyl, (C₂-C₈)-Alkynyl-carbonyl, 1-(Hydroxyimino)-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkylimino-(C₁-C₆)-alkyl, 1-(C₁-C₄)-Alkoxyimino-(C₁-C₆)-alkyl, (C₁-C₈)-Alkyl-carbonylamino, (C₂-C₈)-Alkenyl-carbonylamino, (C₂-C₈)-Alkynyl-carbonylamino, Carbamoyl, (C₁-C₈)-Alkyl-carbamoyl, Di-(C₁-C₆)-Alkyl-carbamoyl, (C₂-C₆)-Alkenyl-carbamoyl, (C₂-C₆)-Alkynyl-carbamoyl, (C₁-C₈)-Alkoxy-carbonylamino, (C₁-C₈)-Alkyl-amino-carbonylamino, (C₁-C₈)-Alkoxy-carbonyloxy, (C₁-C₈)-Alkyl-carbonyloxy, das unsubstituiert oder

durch Halogen, Nitro, (C₁–C₄)-Alkoxy und/oder gegebenenfalls substituiertes Phenyl substituiert ist, (C₂–C₆)-Alkenylcarbonyloxy, (C₂–C₆)-Alkylcarbonyloxy, Phenyl, Phenyl-(C₁–C₆)-alkoxy, Phenyl-(C₁–C₆)-alkoxycarbonyl, Phenoxy, Phenoxy-(C₁–C₆)-alkoxy, Phenoxy-(C₁–C₆)-alkoxycarbonyl, Phenylcarbonyloxy, Phenylcarbonylamino, Phenyl-(C₁–C₆)-alkylcarbonylamino, wobei die
5
letzten genannten 10 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁–C₄)-Alkyl, (C₁–C₄)-Alkoxy, (C₁–C₄)-Halogenalkyl, (C₁–C₄)-Halogenalkoxy und Nitro substituiert sind,

–SiR²R³R⁴, –O–SiR²R³R⁴, R²R³R⁴Si-(C₁–C₆)-alkoxy, –CO–O–NR²R³, –O–N=CR²R³,
–N=CR²R³, O-(CH₂)_m–CH(OR²)OR³, R'O–CHR''–CH(OR')-(C₁–C₆)-alkoxy und der drei- bis sieben-
10
gliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls durch Halogen und/oder (C₁–C₄)-Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

R' unabhängig voneinander (C₁–C₄)-Alkyl, oder paarweise zusammen einen (C₁–C₆)-Alkandiyrest und R'' Wasserstoff oder (C₁–C₄)-Alkyl bedeuten;

R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substitu-
15
iertes (C₁–C₆)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C₂–C₆)-Alkandiykette stehen; und R⁴ Wasserstoff oder gegebenenfalls substituier-
tes (C₁–C₄)-Alkyl, bedeutet, oder

R und R⁴ gemeinsam für eine Alkandiykette mit 2 bis 5 C-Atomen steht, in der eine CH₂-Gruppe gegeben-
20
enfalls durch O, NH oder N(C₁–C₄)-Alkyl ersetzt sein kann;

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁–C₆)-Alkyl
bedeuten;

R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁–C₆)-Alkyl, das
durch Halogen, (C₁–C₄)-Alkoxy oder Phenyl substituiert sein kann, bedeuten;

R⁹ und R¹⁰ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁–C₆)-Alkyl, das
25
durch Halogen, (C₁–C₄)-Alkoxy oder OH substituiert sein kann, bedeuten;

T unabhängig voneinander Sauerstoff oder Schwefel bedeuten; und

m eine ganze Zahl von 0 bis 6 bedeutet;

oder deren Salz.

2. Mittel gemäß Anspruch 1, worin in der Verbindung der Formel I

A (C₁–C₄)-Alkandiy oder (C₃–C₆)-Alkandiy bedeutet,

X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halo-
gen-(C₁–C₆)-alkyl, Halogen-(C₁–C₆)-alkoxy, (C₁–C₆)-Alkyl, (C₁–C₆)-Alkoxy, Nitro, Amino, Cyano,
(C₁–C₆)-Alkylthio oder (C₁–C₆)-Alkylsulfonyl bedeuten;

wobei mindestens ein Rest X für Wasserstoff steht;

n 3 ist;

R Wasserstoff, (C₁–C₁₂)-Alkyl, (C₃–C₈)-Cycloalkyl, (C₂–C₁₂)-Alkenyl, (C₂–C₈)-Alkyl oder
–N=CR²R³ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere
gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen-(C₁–C₈)-al-
koxy, Nitro, Cyano, Hydroxy, (C₁–C₈)-Alkoxy, worin eine oder mehrere CH₂-Gruppen durch Sauerstoff
40
ersetzt sein können, (C₁–C₆)-Alkylthio, (C₁–C₄)-Alkylsulfinyl, (C₁–C₄)-Alkylsulfonyl, (C₂–C₆)-Alkenylthio,
(C₂–C₆)-Alkylthio, (C₂–C₆)-Alkenyloxy, (C₂–C₆)-Alkylloxy, (C₃–C₆)-Cycloalkyl, (C₃–C₆)-Cy-
cloalkoxy, Mono- und Di-(C₁–C₄)-alkylamino, (C₁–C₆)-Alkoxycarbonyl, (C₂–C₆)-Alkenyloxycarbonyl,
(C₂–C₆)-Alkylloxycarbonyl, (C₁–C₆)-Alkylthiocarbonyl, (C₁–C₆)-Alkylcarbonyl, (C₂–C₆)-Alkenylcarbonyl,
45
(C₂–C₆)-Alkylcarbonyl, 1-(Hydroxyimino)-(C₁–C₆)-alkyl, 1-(C₁–C₄)-Alkylimino-(C₁–C₄)-alkyl,
1-(C₁–C₄)-Alkoxyimino-(C₁–C₄)-alkyl, (C₁–C₆)-Alkylcarbonylamino, (C₂–C₆)-Alkenylcarbonylamino,
(C₂–C₆)-Alkylcarbonylamino, Carbamoyl, (C₁–C₆)-Alkylcarbamoyl, Di-(C₁–C₄)-Alkylcarbamoyl,
(C₂–C₆)-Alkenylcarbamoyl, (C₂–C₄)-Alkylcarbamoyl, (C₁–C₆)-Alkoxycarbonylamino, (C₁–C₆)-Alkyl-
amino-carbonylamino, (C₁–C₆)-Alkoxycarbonyloxy, (C₁–C₆)-Alkylcarbonyloxy, das unsubstituiert ist,
50
durch Halogen, Nitro, (C₁–C₄)-Alkoxy und/oder gegebenenfalls substituiertes Phenyl substituiert ist,
(C₂–C₆)-Alkenylcarbonyloxy, (C₂–C₆)-Alkylcarbonyloxy, Phenyl, Phenyl-(C₁–C₄)-alkoxy, Phenyl-
(C₁–C₄)-alkoxycarbonyl, Phenoxy, Phenoxy-(C₁–C₄)-alkoxy, Phenoxy-(C₁–C₄)-alkoxycarbonyl, Phenylcarbonyloxy, Phenylcarbonylamino, Phenyl-(C₁–C₆)-alkylcarbonylamino, wobei die
letzten genannten 10 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene
55
Reste aus der Gruppe enthaltend Halogen, (C₁–C₄)-Alkyl, (C₁–C₄)-Alkoxy, (C₁–C₄)-Halogenalkyl,
(C₁–C₄)-Halogenalkoxy und Nitro substituiert sind, –SiR²R³R⁴, –O–SiR²R³R⁴Si-(C₁–C₄)-al-
koxy, –CO–O–NR²R³, –O–N=CR²R³, –N=CR²R³, O-(CH₂)_m–CH(OR²)OR³, R'O–
CHR''–CH(OR')-(C₁–C₄)-alkoxy und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten
und gegebenenfalls durch Halogen und/oder (C₁–C₄)-Alkyl substituierten gesättigten oder ungesättigten
heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und
60
N;

R² und R³ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substitu-
iertes (C₁–C₄)-Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegeben-
enfalls substituierte (C₂–C₄)-Alkandiykette stehen;

R⁵ und R⁶ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁–C₄)-Alkyl
bedeuten;

R⁷ und R⁸ gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C₁–C₄)-Alkyl, das
durch Halogen, (C₁–C₄)-Alkoxy oder Phenyl substituiert sein kann, bedeuten;

R^9 und R^{10} gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C_1-C_4) -Alkyl, das durch Halogen, (C_1-C_4) -Alkoxy oder OH substituiert sein kann, bedeuten;

m eine ganze Zahl von 0 bis 3 bedeutet;

und die übrigen Reste oder Variablen wie im Anspruch 1 definiert sind.

3. Mittel gemäß Anspruch 1 oder 2, worin in Formel I

A (C_1-C_3) -Alkandiyl oder (C_3-C_8) -Alkendiyl bedeutet,

X wie im Anspruch 2 definiert ist und mindestens 2 Rest X für Wasserstoff stehen;

n 3 ist;

R Wasserstoff, (C_1-C_{12}) -Alkyl, (C_3-C_8) -Cycloalkyl, (C_2-C_{12}) -Alkenyl, (C_2-C_8) -Alkinyl oder $-N=CR^2R^3$ bedeutet, wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Hydroxy, (C_1-C_8) -Alkoxy, worin eine oder mehrere CH_2 -Gruppen durch Sauerstoff ersetzt sein können, (C_1-C_4) -Alkylthio, (C_2-C_4) -Alkenylthio, (C_2-C_4) -Alkinylthio, (C_2-C_4) -Alkenyloxy, (C_2-C_4) -Alkinyloxy, Mono- und Di- (C_1-C_2) -alkylamino, (C_1-C_4) -Alkoxy-carbonyl, (C_2-C_4) -Alkenyloxy-carbonyl, (C_2-C_4) -Alkinyloxy-carbonyl, (C_1-C_4) -Alkyl-carbonyl, (C_2-C_4) -Alkenyl-carbonyl, (C_2-C_4) -Alkinyl-carbonyl, (C_1-C_4) -Alkyl-carbonylamino, (C_2-C_4) -Alkenyl-carbonylamino, Carbamoyl, (C_1-C_8) -Alkylcarbamoyl, Di- (C_1-C_6) -Alkylcarbamoyl, (C_1-C_4) -Alkoxy-carbonyloxy, (C_1-C_4) -Alkyl-carbonyloxy, das unsubstituiert oder durch Halogen und/oder (C_1-C_4) -Alkoxy substituiert ist, (C_2-C_4) -Alkenyl-carbonyloxy, (C_2-C_4) -Alkinyl-carbonyloxy, Phenyl, Phenyl- (C_1-C_4) -alkoxy, Phenyl- (C_1-C_4) -alkoxy-carbonyl, Phenoxy, Phenoxy- (C_1-C_4) -alkoxy, Phenoxy-carbonyl, Phenoxy- (C_1-C_4) -alkoxy-carbonyl, Phenyl-carbonyloxy, wobei die letztgenannten 8 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C_1-C_2) -Alkyl, (C_1-C_2) -Alkoxy, (C_1-C_2) -Halogenalkyl, (C_1-C_2) -Halogenalkoxy und Nitro substituiert sind, $-SiR^2R^3R^4$, $-O-SiR^2R^3R^4$, $R^2R^3R^4Si-(C_1-C_4)$ -alkoxy, $O-N=CR^2R^3$, $-N=CR^2R^3$, $O-(CH_2)_m-CH(OR^2)OR^3$, $R^3O-CHR''-CH(OR^1)-(C_1-C_4)$ -alkoxy, und der drei- bis siebengliedrigen, gegebenenfalls benzokondensierten und gegebenenfalls durch Halogen und/oder (C_1-C_4) -Alkyl substituierten gesättigten oder ungesättigten heterocyclischen Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

R' unabhängig voneinander (C_1-C_4) -Alkyl, oder paarweise zusammen einen (C_1-C_4) -Alkandiylrest und

R'' Wasserstoff oder (C_1-C_4) -Alkyl bedeuten;

R^2 und R^3 gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C_1-C_4) -Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C_2-C_4) -Alkandiylkette stehen; und

R^5 und R^6 gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C_1-C_4) -Alkyl bedeuten;

R^7 und R^8 gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C_1-C_4) -Alkyl, das durch Halogen, (C_1-C_4) -Alkoxy oder Phenyl substituiert sein kann bedeuten;

R^9 und R^{10} gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C_1-C_4) -Alkyl, das durch Halogen, (C_1-C_4) -Alkoxy oder OH substituiert sein kann, bedeuten;

m eine ganze Zahl von 0 bis 2 bedeutet;

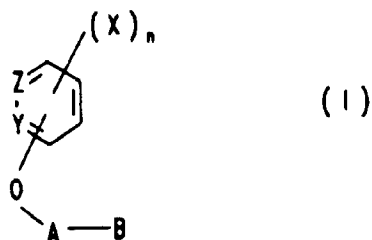
und die übrigen Reste oder Variablen wie im Anspruch 1 oder 2 definiert sind.

4. Verfahren zum Schutz von Kulturpflanzen vor phytotoxischen Nebenwirkungen von Herbiziden, dadurch gekennzeichnet, daß eine wirksame Menge mindestens einer Verbindung der in Anspruch 1 definierten Formel I vor, nach oder gleichzeitig mit dem im Anspruch 1 definierten herbiziden Wirkstoff auf die Pflanzen, Pflanzensamen oder die Anbaufläche appliziert wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Kulturpflanzen Getreidepflanzen oder Maispflanzen sind.

6. Verwendung von Verbindungen der in einem der Ansprüche 1 bis 3 definierten Formel zum Schutz von Kulturpflanzen vor phytotoxischen Nebenwirkungen der wie im Anspruch 1 unter A) definierten herbiziden Wirkstoffe.

7. Verbindung der Formel I,



in welcher

Y und Z gleich oder verschieden sind und unabhängig voneinander CX oder N bedeuten;

X für gleiche oder verschiedene Reste steht, welche unabhängig voneinander Wasserstoff, Halogen, Halogen- (C_1-C_8) -alkyl, Halogen- (C_1-C_8) -alkoxy, (C_1-C_8) -Alkyl, (C_1-C_8) -Alkoxy, Nitro, Amino, Cyano, (C_1-C_8) -Alkylthio oder (C_1-C_8) -Alkylsulfonyl bedeuten;

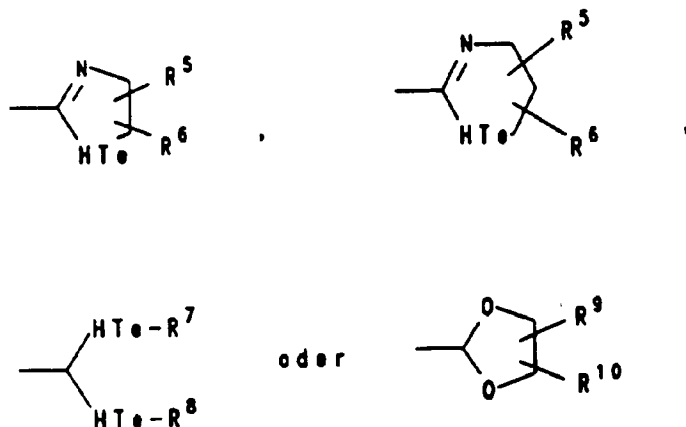
n 3 ist;

R^2 und R^3 gleich oder verschieden sind und unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes (C_1-C_6) -Alkyl oder gegebenenfalls substituiertes Phenyl bedeuten oder gemeinsam für eine gegebenenfalls substituierte (C_1-C_6) -Alkandiyolkette stehen und

A) für den Fall, daß mindestens einer der Reste Y und Z Stickstoff bedeutet, dann A (C_1-C_6) -Alkandiyol oder (C_3-C_8) -Alkandiyol bedeutet;

B einen Rest der Formel

$-COOR$, $-COSR$, $-CONRR^4$,



bedeutet;

R ein Äquivalent eines für die Landwirtschaft geeigneten Kations, (C_3-C_{18}) -Alkyl, (C_3-C_{12}) -Cycloalkyl, (C_3-C_{18}) -Alkenyl, (C_3-C_8) -Alkynyl oder $-N=CR^2R^3$ bedeutet,

wobei jeder der vorstehenden C-haltigen Reste gegebenenfalls einen oder mehrere gleiche oder verschiedene Substituenten trägt aus der Gruppe enthaltend Halogen, Halogen (C_1-C_8) -alkoxy, Nitro, Cyano, Hydroxy, (C_1-C_8) -Alkoxy, worin eine oder mehrere CH_2 -Gruppen durch Sauerstoff ersetzt sein können,

(C_1-C_8) -Alkylthio, (C_1-C_6) -Alkylsulfinyl, (C_1-C_6) -Alkylsulfonyl, (C_2-C_8) -Alkenylthio,

(C_2-C_8) -Alkynylthio, (C_2-C_8) -Alkenyloxy, (C_2-C_8) -Alkynyloxy, (C_3-C_7) -Cycloalkyl,

(C_3-C_7) -Cycloalkoxy, Mono- und Di- (C_1-C_4) -alkylamino, (C_1-C_8) -Alkoxy-carbonyl,

(C_2-C_8) -Alkenyloxycarbonyl, (C_2-C_8) -Alkynyloxycarbonyl, 1-(Hydroxyimino)- (C_1-C_6) -alkyl,

1- (C_1-C_4) -Alkoxyimino- (C_1-C_6) -alkyl, (C_1-C_8) -Alkylcarbonylamino, (C_2-C_8) -Alkenylcarbonylamino,

(C_2-C_8) -Alkynylcarbonylamino, Carbamoyl,

(C_1-C_8) -Alkylcarbonylamino, Di- (C_1-C_6) -Alkylcarbonylamino, (C_2-C_6) -Alkenylcarbonylamino, (C_2-C_6) -Alkynylcarbonylamino,

(C_1-C_8) -Alkoxy-carbonylamino, (C_1-C_8) -Alkyl-amino-carbonylamino,

(C_1-C_8) -Alkoxy-carbonyloxy, (C_1-C_8) -Alkylcarbonyloxy, das unsubstituiert oder durch Halogen, Nitro, (C_1-C_4) -Alkoxy und/oder gegebenenfalls substituiertes Phenyl substituiert ist, (C_2-C_6) -Alkenylcarbonyloxy, (C_2-C_6) -Alkynylcarbonyloxy, Phenyl, Phenyl- (C_1-C_6) -alkoxy, Phenyl- (C_1-C_6) -alkoxy-carbonyl, Phenoxy, Phenoxy- (C_1-C_6) -alkoxy, Phenoxy- (C_1-C_6) -alkoxy-carbonyl, Phenylcarbonyloxy, Phenylcarbonylamino, Phenyl- (C_1-C_6) -alkylcarbonylamino, wobei die letztgenannten 9 Reste im Phenylring unsubstituiert oder ein- oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C_1-C_4) -Alkyl, (C_1-C_4) -Alkoxy, (C_1-C_4) -Halogenalkyl, (C_1-C_4) -Halogenalkoxy und Nitro substituiert sind, $-SiR^2R^3R^4$, $-O-SiR^2R^3R^4$, $R^2R^3R^4Si-(C_1-C_6)$ -alkoxy, $-CO-O-NR^2R^3$, $-O-N=CR^2R^3$, $-N=CR^2R^3$ und $O-(CH_2)_m-CH(OR^2)OR^3$, $R'O-CH(R'')-CH(OR')-(C_1-C_6)$ -alkoxy, und der drei- bis siebengliedrige, gegebenenfalls benzokondensierte und gegebenenfalls durch Halogen und/oder (C_1-C_4) -Alkyl substituierte gesättigte oder ungesättigte heterocyclische Reste mit bis zu drei gleichen oder verschiedenen Heteroatomen aus der Reihe S, O und N;

R' unabhängig voneinander (C_1-C_4) -Alkyl, oder paarweise zusammen einen (C_1-C_6) -Alkandiyolrest und

R'' Wasserstoff oder (C_1-C_4) -Alkyl bedeuten,

R^4 Wasserstoff oder gegebenenfalls substituiertes (C_1-C_4) -Alkyl bedeutet; oder

R und R' gemeinsam für eine Alkanidylkette mit 2 bis 5 C-Atomen steht, in der eine CH_2 -Gruppe gegebenenfalls durch O, NH oder N (C_1-C_4) -Alkyl ersetzt sein kann, und

R^5 und R^6 unabhängig voneinander Wasserstoff oder (C_1-C_6) -Alkyl bedeuten; R^7 und R^8 unabhängig voneinander Wasserstoff oder (C_1-C_6) -Alkyl, das durch Halogen, (C_1-C_4) -Alkoxy oder Phenyl substituiert sein kann, bedeuten und

R^9 und R^{10} gleich oder verschieden sind und unabhängig voneinander Wasserstoff oder (C_1-C_6) -Alkyl, das durch Halogen, (C_1-C_4) -Alkoxy oder OH substituiert sein kann, bedeuten;

T unabhängig voneinander Sauerstoff oder Schwefel bedeuten, und

m eine ganze Zahl von 0 bis 6 bedeutet,

B) oder für den Fall, daß keiner der Reste Y und Z Stickstoff bedeutet, dann

A (C_1-C_6) -Alkandiyol oder (C_4-C_8) -Alkandiyol bedeutet;

B ein Rest der Formel

—COOR, —COSR oder —CONRR⁴ bedeutet;

R (C₁—C₁₈)-Alkyl, (C₃—C₁₂)-Cycloalkyl, (C₂—C₁₈)-Alkenyl oder (C₂—C₈)-Alkynyl bedeutet,

wobei jeder der vorstehenden C-haltigen Reste einen oder mehrere gleiche oder verschiedene Reste trägt aus der Gruppe enthaltend (C₂—C₈)-Alkenylthio, (C₂—C₈)-Alkynylthio, (C₂—C₈)-Alkenyloxy, (C₂—C₈)-Alkynyloxy, (C₃—C₇)-Cycloalkyl, (C₃—C₇)-Cycloalkoxy, (C₇—C₁₀)-Alkenyloxycarbonyl, (C₃—C₈)-Alkynyloxycarbonyl, (C₁—C₈)-Alkylthiocarbonyl, (C₂—C₈)-Alkenylcarbonyl, (C₂—C₆)-Alkynylcarbonyl, 1-(Hydroxyimino)-(C₁—C₆)-alkyl, 1-(C₁—C₄)-Alkylimino-(C₁—C₆)-alkyl, 1-(C₁—C₄)-Alkoxyimino-(C₁—C₆)-alkyl, (C₁—C₈)-Alkylcarbonylamino, (C₂—C₈)-Alkenylcarbonylamino, (C₂—C₈)-Alkynylcarbonylamino, Carbamoyl, (C₁—C₈)-Alkylcarbamoyl, Di-(C₁—C₆)-Alkylcarbamoyl, (C₂—C₆)-Alkenylcarbamoyl, (C₂—C₆)-Alkynylcarbamoyl, (C₁—C₈)-Alkoxycarbonylamino, (C₁—C₈)-Alkyl-amino-carbonylamino, (C₁—C₈)-Alkoxycarbonyloxy, (C₁—C₈)-Alkylcarbonyloxy, das unsubstituiert und/oder durch Halogen, Nitro, (C₁—C₄)-Alkoxy oder gegebenenfalls substituiertes Phenyl substituiert ist, (C₂—C₈)-Alkenylcarbonyloxy, (C₂—C₆)-Alkynylcarbonyloxy, Phenyl-(C₂—C₆)-alkoxy, Phenyl-(C₂—C₆)-alkoxycarbonyl, Phenoxy-(C₁—C₆)-alkoxy, Phenoxy-(C₂—C₆)-alkoxycarbonyl, Phenylcarbonyloxy, Phenylcarbonylamino, Phenyl-(C₁—C₆)-alkylcarbonylamino, wobei die letztgenannten 7 Reste im Phenylring unsubstituiert oder ein oder mehrfach durch gleiche oder verschiedene Reste aus der Gruppe enthaltend Halogen, (C₁—C₄)-Alkyl, (C₁—C₄)-Alkoxy, (C₁—C₄)-Halogenalkyl, (C₁—C₄)-Halogenalkoxy und Nitro substituiert sind,

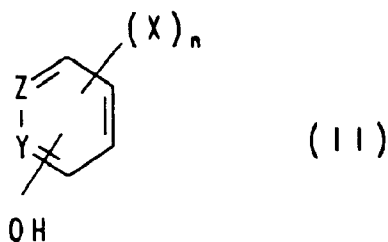
—SiR²R³R⁴, —O—SiR²R³R⁴, R²R³R⁴Si-(C₁—C₆)-alkoxy, —CO—O—NR²R³, —O—N=CR²R³, —N=CR²R³ und O-(CH₂)_m-CH(OR²OR³), und R'O—CHR''—CH(OR')-(C₁—C₆)-alkoxy;

R' unabhängig voneinander (C₁—C₄)-Alkyl, oder paarweise zusammen einen (C₁—C₆)-Alkandiylrest und R'' Wasserstoff oder (C₁—C₄)-Alkyl bedeuten,

R⁴ Wasserstoff oder gegebenenfalls substituiertes (C₁—C₄)-Alkyl bedeutet; und

m eine ganze Zahl von 0 bis 6 bedeutet.

8. Verfahren zur Herstellung einer Verbindung der Formel, dadurch gekennzeichnet, daß man eine Verbindung der Formel II



worin

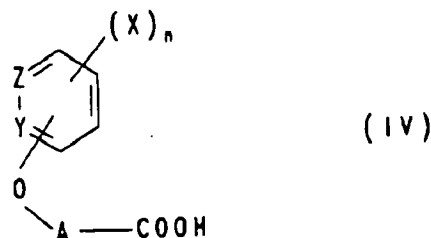
Z, Y, X, n, A und B wie in Formel I definiert sind mit einem Alkancarbonsäurederivat der Formel III,

W—A—B (III),

worin

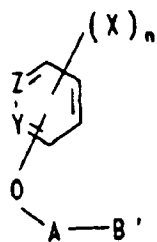
W eine Abgangsgruppe bedeutet, umsetzt;

eine Aryl- oder Heteroaryloxycarbonsäure der Formel IV



worin Z, Y, X, n und A wie in Formel I definiert sind, mit Mercaptanen, Aminen oder Alkoholen umsetzt, oder

ein Aryl- oder Heteroaryloxycarbonsäurederivat der Formel V,



(v)

5

10

worin

Z, Y, X, n und A wie in Formel I definiert sind und B' eine Alkoxycarbonylgruppe, bedeutet, mit Alkoholen oder Aminen umestert bzw. amidiert, und die so erhaltenen Verbindungen der Formel I gegebenenfalls in ihr Salz überführt.

15

9. Herbizides Mittel, enthaltend mindestens eine Verbindung der Formel I gemäß Anspruch 7.

10. Mittel gemäß Anspruch 9, welches zusätzlich einen herbiziden Wirkstoff enthält.

11. Verfahren zum Schutz von Kulturpflanzen vor phytotoxischen Nebenwirkungen von Herbiziden, dadurch gekennzeichnet, daß eine wirksame Menge mindestens einer Verbindung gemäß Anspruch 7 vor, nach oder gleichzeitig mit einem herbiziden Wirkstoff auf die Pflanzen, Pflanzensamen oder die Anbaufläche appliziert wird.

20

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß die Kulturpflanzen Getreidepflanzen oder Maispflanzen sind.

13. Verwendung einer Verbindung gemäß Anspruch 7 zum Schutz von Kulturpflanzen vor phytotoxischen Nebenwirkungen herbizider Wirkstoffe.

25

14. Mit mindestens einer Verbindung der Formel I gemäß Anspruch 7 gebeiztes Saatgut.

30

35

40

45

50

55

60

65



①9 BUNDESREPUBLIK
DEUTSCHLAND



DEUTSCHES
PATENTAMT

①2 **Offenlegungsschrift**
①0 **DE 40 17 019 A 1**

⑤1 Int. Cl.⁵:
A61 K 31/135

②1 Aktenzeichen: P 40 17 019.5
②2 Anmeldetag: 26. 5. 90
④3 Offenlegungstag: 28. 11. 91

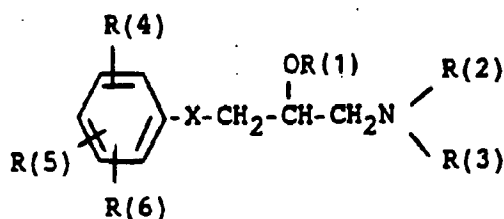
DE 40 17 019 A 1

⑦1 Anmelder:
Hoechst AG, 6230 Frankfurt, DE

⑦2 Erfinder:
Kottmann, Hariolf, Dr., 6238 Hofheim, DE; Hänel,
Heinz, Dr., 6370 Oberursel, DE; Kirsch, Reinhard, Dr.,
6230 Frankfurt, DE

⑤4 Verwendung von substituierten β -Hydroxyethylaminen als potente Hemmstoffe der Exoenzyme von Pilzen

⑤7 Verbindungen der Formel I



die als β -Blocker bereits bekannt sind, dienen zur Vorbeu-
gung gegen Pilzerkrankungen und zur Behandlung von
Pilzerkrankungen.

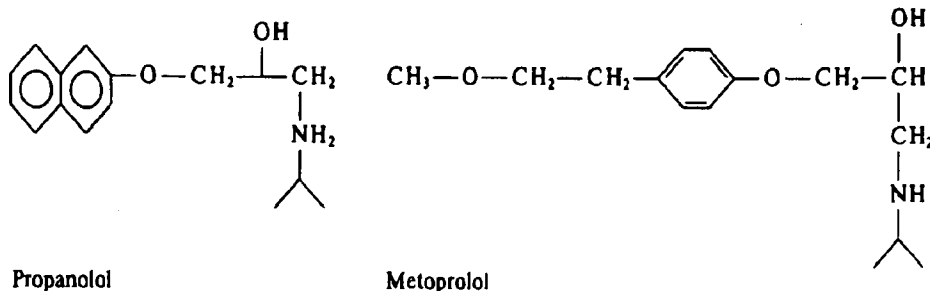
R(1) ist darin Alk(en)yl oder Benzyl,
R(2) und R(3) sind (Cyclo)Alk(en)yl, (Di)Phenyl(alk)(en)yl
oder gemeinsam eine $(CH_2)_m$ -Kette,
R(3), R(5) und R(6) können eine Vielzahl von bei derartigen
 β -Blockern üblichen Substituenten sein.

DE 40 17 019 A 1

Beschreibung

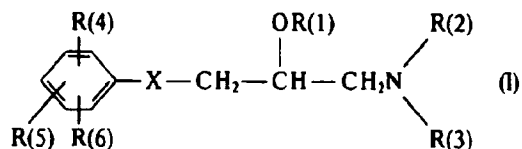
Die Erfindung betrifft die Verwendung von substituierten β -Hydroxyethylaminen und von solchen Verbindungen enthaltende pharmazeutischen Zusammensetzungen als Pharmazeutika, insbesondere als Wachstumshemmer der pathogenen Phase dimorpher Hefezellen, als Antimykotika und Pflanzenschutzmittel, z. B. Fungizide und Wachstumsregulatoren, wobei die Verwendung der Verbindungen sowohl in der Prophylaxe als auch in der Therapie stattfinden kann.

Von einigen β -Hydroxyethylaminen, welche als Betablocker verwendet werden, ist bekannt, daß sie eine allerdings geringe Wirkung auf die Inhibierung der liposomalen Phospholipase A1 von Säugern besitzen. (vgl. K. Y. Hostetler et al, Biochemical Pharmacology 34, 521–524 (1985)). Wirkungsstärke und Verträglichkeit dieser Verbindungen sind jedoch nicht zufriedenstellend. (Beispiele sind Propranolol oder Metoprolol).



Es wurde nun überraschenderweise gefunden, daß substituierte β -Hydroxyethylamine, in Abhängigkeit von der Struktur der jeweiligen Substituenten, potente Hemmstoffe der Exoenzyme (Pathogenitätsfaktoren) von Pilzen sind, fungizide sowie antimykotische Wirkung aufweisen und insbesondere hervorragende Wachstumshemmer der pathogenen Phase dimorpher Hefen sind.

Die Erfindung betrifft daher die Verwendung von substituierten β -Hydroxyethylaminen sowie diese Verbindungen enthaltende pharmazeutische Zusammensetzungen der Formel I



zur Vorbeugung gegen und Behandlung von Pilzerkrankungen; in den Verbindungen bedeuten:

R(1) H, (C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Benzyl (unsubstituiert oder ein- oder mehrfach substituiert durch F, Cl, Br, CF₃, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), OCH₃, O-Phenyl oder Phenyl)

R(2) H, (C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₁₀)-Cycloalkyl, Phenyl-(C₁–C₆) Alkyl (geradkettig oder verzweigt), Phenyl-(C₂–C₆)-Alkenyl (geradkettig oder verzweigt, ein- oder zweifach ungesättigt), Diphenyl-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert oder ein- oder mehrfach substituiert ist durch Substituenten aus der Gruppe F, Cl, Br, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₃–C₆)-Cycloalkyl, OH, SH, (C₁–C₁₀)-Akoxy (geradkettig oder verzweigt), Phenyl, Benzyl, Phenethyl, Thiophenyl, C_nF_{2n+1} mit n = 1–6),

R(3) wie R(2) definiert ist, wobei R(2) und R(3) jeweils gleiche oder verschiedene Bedeutung aufweisen, oder

R(2) mit R(3) eine Kette (CH₂)_m mit m gleich 4–6 bildet, in welcher eine CH₂-Gruppe durch O, S oder N ersetzt sein kann, wobei N als weiteren Bindungspartner ein H-Atom, eine CH₃, Phenyl-, Benzyl oder Phenethylgruppe trägt, und

R(4) H, (C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₂₀)-Cycloalkyl [mono-, bi- oder multicyclisch, unsubstituiert oder ein- oder zweifach mit (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt), C_nF_{2n+1} (mit n gleich 1–4), F, Cl, Br, OH substituiert], wie z. B. Norbornyl, Adamantyl, Decahydronaphthalinyl; Y-(C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), Y-(C₂–C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y-(C₃–C₂₀)-Cycloalkyl (mono-, bi- oder multicyclisch, unsubstituiert oder wie oben angegeben substituiert), Phenyl, Y-Phenyl, Phenyl-(C₁–C₂)-Alkyl, Biphenyl, F, Cl, Br, I, C_nF_{2n+1} (mit n gleich 1–8), CCl₃, YH, Naphthyl, CN, NO₂, mit Y gleich Sauerstoff oder Schwefel

und R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind, und

R(4) mit R(5), für den Fall, daß die Substituenten an benachbarten Positionen am Phenylring gebunden sind,

gemeinsam eine $(CH_2)_p$ -Kette mit p gleich 3 oder 4 bilden können,

und

R(6) H, (C_1-C_{15}) -Alkyl (geradkettig oder verzweigt), (C_2-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y- (C_1-C_{15}) -Alkyl (geradkettig oder verzweigt), Y- (C_2-C_{15}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Phenyl, Y-Phenyl, Benzyl, Biphenyl, F, Cl, Br, I, C_nF_{2n+1} (mit n gleich 1–8), CCl_3 , Naphthyl, YH

Y = Sauerstoff, Schwefel

X = Sauerstoff, Schwefel, SO, SO_2 ,

und ihre Salze mit pharmazeutisch akzeptablen Säuren.

Bevorzugt sind Verbindungen des Typs I, in denen die Substituenten folgende Bedeutung besitzen:

R(1) H, (C_1-C_8) -Alkyl (geradkettig oder verzweigt), (C_3-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Benzyl (unsubstituiert oder einfach oder zweifach substituiert durch F, Cl, CF_3 , (C_1-C_4) -Alkyl (geradkettig oder verzweigt), OCH_3 ,

R(2) H, (C_1-C_8) -Alkyl (geradkettig oder verzweigt), (C_3-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Phenyl- (C_1-C_6) -Alkyl (geradkettig oder verzweigt), Diphenyl- (C_1-C_6) -Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert oder ein- oder zweifach substituiert ist durch Substituenten aus der Gruppe OH, F, Cl, Br, (C_1-C_4) -Alkyl (geradkettig oder verzweigt), (C_1-C_4) -Alkoxy (geradkettig oder verzweigt), Phenyl, Benzyl, Phenethyl,

R(3) wie R(2) definiert ist, wobei R(2) und R(3) jeweils gleiche oder verschiedene Bedeutung aufweisen,

oder

R(2) mit R(3) eine Kette $(CH_2)_m$ - mit m gleich 4–6 bildet, in welcher eine CH_2 -Gruppe durch ein Sauerstoff oder Stickstoff-Atom ersetzt sein kann, wobei N als weiteren Bindungspartner ein H-Atom, eine CH_3 , Phenyl-, Benzyl oder Phenethylgruppe trägt,

und

R(4) H, (C_1-C_{15}) -Alkyl (geradkettig oder verzweigt), (C_2-C_{15}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C_3-C_{15}) -Cycloalkyl [mono-, bi- oder multicyclisch, unsubstituiert oder einfach mit (C_1-C_4) -Alkyl (geradkettig oder verzweigt), (C_1-C_4) -Alkoxy (geradkettig oder verzweigt), substituiert], wie z. B. Norbornyl, Adamantyl, Decahydronaphthalinyl; Y- (C_1-C_{10}) -Alkyl (geradkettig oder verzweigt), Y- (C_2-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y- (C_3-C_{15}) -Cycloalkyl (mono-, bi- oder multicyclisch, unsubstituiert oder wie oben angegeben substituiert), Phenyl, Y-Phenyl, Phenyl- (C_1-C_2) -Alkyl, Biphenyl, F, Cl, C_nF_{2n+1} (mit n gleich 1–4), CCl_3 , Naphthyl, CN, mit Y gleich Sauerstoff oder Schwefel

und

R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind,

und

R(4) mit R(5), für den Fall, daß die Substituenten an benachbarten Positionen am Phenylring gebunden sind, gemeinsam eine $(CH_2)_p$ -Kette mit p gleich 3 oder 4 bilden können,

und

R(6) H, (C_1-C_{10}) -Alkyl (geradkettig oder verzweigt), Y- (C_1-C_{10}) -Alkyl (geradkettig oder verzweigt), Y- (C_2-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder zweifach ungesättigt), Phenyl, Benzyl, Biphenyl, F, Cl, Br, C_nF_{2n+1} (mit n gleich 1–4), CCl_3 , Naphthyl,

Y = Sauerstoff, Schwefel

X = Sauerstoff, Schwefel

und ihre Salze mit pharmazeutisch akzeptablen Säuren.

Besonders bevorzugt sind Verbindungen I, bei denen die Substituenten folgende Bedeutung haben:

R(1) H, (C_1-C_8) -Alkyl (geradkettig oder verzweigt), Benzyl (unsubstituiert oder ein- oder zweifach substituiert durch F, Cl, CF_3 , (C_1-C_4) -Alkyl (geradkettig oder verzweigt), OCH_3 ,

R(2) H, (C_1-C_8) -Alkyl (geradkettig oder verzweigt), (C_3-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder zweifach ungesättigt), Phenyl- (C_1-C_6) -Alkyl (geradkettig oder verzweigt), Diphenyl- (C_1-C_6) -Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert oder ein- oder zweifach substituiert ist durch Substituenten aus der Gruppe OH, F, Cl, Br, (C_1-C_4) -Alkyl (geradkettig oder verzweigt), (C_1-C_4) -Alkoxy (geradkettig oder verzweigt), Phenyl, Benzyl,

R(3) H

oder

R(2) gemeinsam mit R(3) eine Kette $(CH_2)_m$ - mit m gleich 4–5 bildet, in welcher eine CH_2 -Gruppe durch ein Sauerstoff- oder Stickstoff-Atom ersetzt sein kann, wobei der Stickstoff als weiteren Bindungspartner ein H-Atom, eine CH_3 , Phenyl-, Benzyl oder Phenethylgruppe trägt,

und

R(4) H, (C_1-C_{10}) -Alkyl (geradkettig oder verzweigt), (C_2-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C_3-C_{15}) -Cycloalkyl [mono-, bi- oder multicyclisch (wie z. B. Norbornyl, Adamantyl, Decahydronaphthalinyl, Y- (C_1-C_{10}) -Alkyl (geradkettig oder verzweigt), Y- (C_2-C_{10}) -Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y- (C_3-C_{15}) -Cycloalkyl (mono-, bi- oder multicyclisch), Phenyl, Y-Phenyl, Benzyl, Biphenyl, F, Cl, C_nF_{2n+1} (mit n gleich 1–4), Naphthyl, CN, mit Y gleich Sauerstoff oder Schwefel,

und

R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind,

und

R(6) H, (C_1-C_4) -Alkyl (geradkettig oder verzweigt), Y- (C_1-C_4) -Alkyl (geradkettig oder verzweigt), F, Cl, CF_3

Y = Sauerstoff, Schwefel

X = Sauerstoff

und ihre Salze mit pharmazeutisch akzeptablen Säuren.

Ganz besonders bevorzugt sind Verbindungen I, bei denen die Substituenten folgende Bedeutung haben:

- 5 R(1) H, Benzyl,
 R(2) H, (C₁–C₈)-Alkyl (geradkettig oder verzweigt), Phenyl-(C₁–C₄)-Alkyl (geradkettig oder verzweigt), wobei das Phenylsystem unsubstituiert oder einfach substituiert ist durch F, Cl, Br, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt),
 R(3) H,
 10 R(4) H, (C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₁₅)-Cycloalkyl [mono-, bi- oder multicyclisch, wie z. B. Norbornyl, Adamantyl, Decahydronaphthalinyl], Y-(C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₃–C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch), Phenyl, Y-Phenyl, Benzyl, Biphenyl, F, Cl, C_nF_{2n+1} (mit n gleich 1–4), mit Y gleich Sauerstoff
 15 und
 R(5) H, (C₁–C₆)-Alkyl (geradkettig oder verzweigt), (C₂–C₆)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₆)-Cycloalkyl Y-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Y-(C₃–C₆)-Cycloalkyl, Phenyl, Y-Phenyl, Benzyl, F, Cl, CF₃
 mit Y gleich Sauerstoff,
 20 R(6) H,
 X gleiche Sauerstoff
 und ihre Salze mit pharmazeutisch akzeptablen Säuren.

Die Erfindung betrifft die Verwendung der Verbindungen I in Form der freien Base oder eines Säureadditionssalzes als potente Hemmstoffe der Exoenzyme von Pilzen.

- 25 Beispiele pharmazeutisch akzeptabler salzbildender Säuren sind anorganische Säuren wie Salzsäure, Bromwasserstoffsäure, Jodwasserstoffsäure, Schwefelsäure, Phosphorsäure oder Salpetersäure oder organische Säuren wie Malonsäure-, Oxalsäure, Gluconsäure, Camphersulfonsäure, Benzolsulfonsäure, Essigsäure, Propionsäure, p-Toluolsulfonsäure oder Salicylsäure.

- Die Verbindungen I weisen mindestens ein asymmetrisches C-Atom auf und können daher als Enantiomere und Diastereomere auftreten. Die Erfindung umfaßt sowohl die Verwendung der reinen Isomeren als auch von deren Gemischen. Gemische von Diastereomeren können nach gebräuchlichen Methoden, z. B. durch selektive Kristallisation aus geeigneten Lösungsmitteln oder durch Chromatographie an Kieselgel oder Aluminiumoxid in die Komponenten aufgetrennt werden.

- Racemate können nach üblichen Methoden in die Enantiomeren aufgetrennt werden, z. B. durch Salzbildung mit einer optisch aktiven Säure, Trennung der diastereomeren Salze und Freisetzung der reinen Enantiomeren mittels einer Base. Darüber hinaus lassen sich die Enantiomeren auch mittels Chromatographie an chiralen Phasen oder auf enzymatischem Wege trennen.

- Die Verbindungen der Formel I, ihre Säureadditionssalze und ihre physiologisch hydrolysierbaren Derivate sind wertvolle Arzneimittel. Sie wirken insbesondere antimikrobiell und eignen sich zur Vorbeugung gegen und Behandlung von Pilzinfektionen beim Menschen und bei verschiedenen Säugetierarten.

- Die Verbindungen sind in vitro sehr gut wirksam gegen Hautpilze, wie z. B. *Trichophyton mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*; gegen Schimmelpilze, wie z. B. *Aspergillus niger* oder gegen Hefen, wie z. B. *Candida albicans*, *C. tropicalis*, *Torulopsis glabrata* und *Trichosporon cutaneum* oder gegen Protozoen wie *Trichomonas vaginalis* oder *T. fetus*, oder auch gegen grampositive und gramnegative Bakterien.

- 45 Auch in vivo, z. B. bei der experimentellen Nierencandidose der Maus, besitzen die Verbindungen nach oraler oder parenteraler Anwendung einen sehr guten systemischen Effekt, z. B. gegen *Candida albicans*. Hierbei wird von der Hefe *Candida albicans* insbesondere das Exoenzymsystem dergestalt beeinflusst, daß die Pathogenität der Erreger deutlich absinkt. Ebenso besteht ein sehr guter Effekt gegen verschiedene Erreger der Hautmykosen (z. B. *Trichophyton mentagrophytes*) am Meerschweinchen nach oraler, parenteraler oder lokaler Anwendung.

Als Indikationsgebiete in der Humanmedizin können beispielsweise genannt werden:

- Dermatomykosen und Systemmykosen durch *Trichophyton mentagrophytes* und andere *Trichophyton*-arten, Mikrosporenarten, *Epidermophyton floccosum*, und biphasische Pilze sowie Schimmelpilze hervorgerufen. Insbesondere werden tiefe Mykosen, die durch *Candida albicans* hervorgerufen werden, günstig beeinflusst, da 55 hierbei ein Eindringen der Pilze in die Wirtszelle verhindert bzw. erschwert wird.

Als Indikationsgebiete in der Tiermedizin können beispielsweise aufgeführt werden:

Alle Dermatomykosen und Systemmykosen, insbesondere solche, die durch die oben genannten Erreger hervorgerufen werden.

- Zur vorliegenden Erfindung gehören pharmazeutische Zubereitungen, die neben nicht toxischen, inerten pharmazeutisch geeigneten Trägerstoffen einen oder mehrere Wirkstoffe enthalten oder die aus einem oder mehreren erfindungsgemäß verwendeten Wirkstoffen bestehen sowie Verfahren zur Herstellung dieser Zubereitungen.

Unter nicht toxischen, inerten pharmazeutisch geeigneten Trägerstoffen sind feste, halbfeste oder flüssige Verdünnungsmittel, Füllstoffe und Formulierungshilfsmittel jeder Art zu verstehen.

- 65 Ein Hemmstoff für die unterschiedlichen Phospholipasen von *Candida albicans* muß im Patienten überall dort in hinreichenden Konzentrationen vorliegen, wo der Pilz die Parenchyme besiedeln kann. Dieser Umstand setzt voraus, daß die entsprechenden Substanzen in einer Konzentration verabreicht werden müssen, die sich zuvor in Tierexperimenten als wirksam erwiesen hat.

Bei den schweren Krankheitsbildern der tiefen Candidose befinden sich die Patienten meist in einem sehr schlechten Allgemeinzustand. Hohes Fieber und weitere Erkrankungen sind häufig anzutreffen. Bei den Dosierungsvorgaben muß zwischen der prophylaktischen Gabe und der Therapie im nachgewiesenen Infektionsfall unterschieden werden. Bei der Prophylaxe kann von einem besseren Allgemeinzustand der Patienten ausgegangen werden, der eine orale Verabreichung ermöglicht. Hierbei können Tabletten, Lösungen, Gele oder Trocken-

saft zum Einsatz kommen. Bei den Formen mit nachgewiesenen tiefen Candidosen muß oft davon ausgegangen werden, daß eine geregelte orale Aufnahme der Wirkstoffe nicht immer gewährleistet ist. Hierfür kommen dann parenterale Anwendungsformen in Frage. Im Ausnahmefall kann auch an eine subcutane Verabreichung gedacht werden.

Als Kandidaten für eine Prophylaxe kommen in erster Linie immunkomprimierte Patienten in Frage, die durch entsprechende medikamentöse Belastung oder durch körpereigene Immunprobleme in dieser Situation sind. Dies sind insbesondere Transplantationspatienten, Zuckerkrankte und/oder adipöse Patienten, AIDS-Patienten, unter Chemotherapie stehende Patienten, Langzeitbeatmete usw.

Die Verbindungen zeigen Hemmungen der Phospholipase von *Candida albicans*, die weit unter den in vitro festgestellten minimalen inhibitorischen Konzentrationen der Wirkstoffe gegenüber *Candida albicans* liegen. Daher kann die Dosierung im Regelfall unter derjenigen liegen, die für eine reine antimykotische Therapie nötig wäre.

Die Wirkung im Patienten beruht darauf, daß die Wirkstoffe bei den *Candida* Zellen, die sich in der Nähe der Parenchyme befinden, zwei unterschiedliche Effekte auslöst. Zum einen wird die Adhäsion der Hefezellen an die Körperzellen verhindert und zum anderen wird *Candida albicans* daran gehindert, die Körperzellen mit Keimschläuchen zu penetrieren. Durch dieses duale Wirkungskonzept kann die Hefe ihre Pathogenität nicht zur vollen Ausprägung bringen. Allerdings muß erwähnt werden, daß *Candida albicans* außer den Phospholipasen noch weitere Pathomechanismen wie z. B. die Protease besitzt. In Anheftung an körpereigene Zellen ist jedoch der primäre Schritt zur Penetration. Da diese Anheftung durch Phospholipasehemmer verhindert wird, können die anderen Pathomechanismen nicht voll zur Geltung kommen.

Als Darreichungsformen kommen beispielsweise Tabletten, Dragees, Kapseln, Pillen, wäßrige Lösungen, Suspensionen und Emulsionen, gegebenenfalls sterile injizierbare Lösungen, nichtwäßrige Emulsionen, Suspensionen und Lösungen, Salben, Cremes, Pasten, Lotions, Sprays etc. in Betracht.

Die prophylaktisch und therapeutisch wirksamen Verbindungen sollen in den oben aufgeführten pharmazeutischen Zubereitungen vorzugsweise in einer Konzentration von etwa 0,1 bis 99,5, vorzugsweise von etwa 0,5 bis 95 Gew.-% der Gesamtmischung vorhanden sein.

Die oben aufgeführten pharmazeutischen Zubereitungen können außer den erfindungsgemäß verwendeten Wirkstoffen auch weitere pharmazeutische Wirkstoffe enthalten.

Die Herstellung der oben aufgeführten pharmazeutischen Zubereitungen erfolgt in üblicher Weise nach bekannten Methoden, z. B. durch Mischen des Wirkstoffs oder der Wirkstoffe mit dem Trägerstoff oder den Trägerstoffen.

Zur vorliegenden Erfindung gehört die Verwendung der erfindungsgemäßen Wirkstoffe sowie von pharmazeutischen Zubereitungen, die einen oder mehrere erfindungsgemäße Wirkstoffe enthalten, in der Human- und Veterinärmedizin zur Verhütung, Besserung und/oder Heilung der oben angeführten Erkrankungen.

Die Wirkstoffe oder die pharmazeutischen Zubereitungen können lokal, oral, parenteral, intraperitoneal und/oder rectal appliziert werden.

Im allgemeinen hat es sich sowohl in der Human- als auch in der Veterinärmedizin als vorteilhaft erwiesen, den oder die erfindungsgemäß verwendeten Wirkstoffe in Gesamtmengen von mindestens etwa 0,05, vorzugsweise 0,1, insbesondere 0,5 mg/kg Körpergewicht bis höchstens etwa 200, vorzugsweise bis 100, insbesondere bis 10 mg/kg Körpergewicht je 24 Stunden, gegebenenfalls in Form mehrerer Einzelgaben zur Erzielung der gewünschten Ergebnisse zu verabreichen. Die Gesamtmenge wird in 1 bis 8, vorzugsweise in 1 bis 3 Einzeldosen, bei tiefen Mykosen jedoch über wesentlich längere Zeiträume (bis zu 6 Wochen) verabreicht.

Es kann jedoch erforderlich sein, von den genannten Dosierungen abzuweichen, und zwar in Abhängigkeit von der Art und dem Körpergewicht des zu behandelnden Objekts, der Art und der Schwere der Erkrankung, der Art der Zubereitung und der Applikation des Arzneimittels sowie dem Zeitraum bzw. Intervall, innerhalb welchem die Verabreichung erfolgt. So kann es in einigen Fällen ausreichend sein, mit weniger als der oben genannten Menge Wirkstoff auszukommen, während in anderen Fällen die oben angeführte Wirkstoffmenge überschritten werden muß. Die Festlegung der jeweils erforderlichen optimalen Dosierung und Applikationsart der Wirkstoffe kann durch jeden Fachmann aufgrund seines Fachwissens leicht erfolgen.

Die Verbindungen der Formel I sind auch als Biozide wirksam. Sie zeichnen sich insbesondere durch ihre fungizide Wirksamkeit bei phytopathogenen Pilzen aus. Selbst bereits in das pflanzliche Gewebe eingedrungene pilzliche Krankheitserreger lassen sich erfolgreich bekämpfen. Dies ist besonders wichtig und vorteilhaft bei solchen Pilzkrankheiten, die nach eingetretener Infektion mit den sonst üblichen Fungiziden nicht mehr wirksam bekämpft werden können. Das Wirkungsspektrum der Verbindungen I erfaßt eine Vielzahl verschiedener phytopathogener Pilze, wie z. B. *Piricularia oryzae*, *Plasmopara viticola*, verschiedene Rostarten, vor allem aber *Venturia inaequalis*, *Cercospora beticola* und echte Mehltäupilze im Obst-, Gemüse-, Getreide- und Zierpflanzenbau.

Die Verbindungen können als Spritzpulver, emulgierbare Konzentrate, versprühbare Lösungen, Stäubemittel, Beizmittel, Dispersionen, Granulate oder Mikrogranulate in den üblichen Zubereitungen angewendet werden.

Unter Spritzpulvern werden in Wasser gleichmäßig dispergierbare Präparate verstanden, die neben dem Wirkstoff außer gegebenenfalls einem Verdünnungs- oder Inertstoff noch Netzmittel, z. B. polyoxethylierte Alkylphenole, polyoxethylierte Fettalkohole, Alkyl- oder Alkylphenylsulfonate und Dispergiermittel, z. B. ligninsulfonsaures Natrium, 2,2'-dinaphthylmethan-6,6'-di-sulfonsaures Natrium, dibutyl-naphthalinsulfonsaures Natri-

um oder auch oleoymethyltaurinsaures Natrium enthalten. Ihre Herstellung erfolgt in üblicher Weise, z. B. durch Mahlen und Vermischen der Komponenten.

Emulgierbare Konzentrate können z. B. durch Auflösen des Wirkstoffes in einem inerten organischen Lösungsmittel, z. B. Butanol, Cyclohexanon, Dimethylformamid, Xylol oder auch höhersiedenden Aromaten oder Kohlenwasserstoffen unter Zusatz von einem oder mehreren Emulgatoren hergestellt werden. Bei flüssigen Wirkstoffen kann der Lösungsmittelanteil auch ganz oder teilweise entfallen. Als Emulgatoren können beispielsweise verwendet werden:

alkylarylsulfonsaure Calciumsalze, wie Ca-dodecylbenzolsulfonat, oder nicht ionische Emulgatoren wie Fettsäurepolyglykolester, Alkylarylpolyglykolether, Fettalkoholpolyglykolether, Propylenoxid-Ethylenoxid-Kondensationsprodukte, Fettalkohol-Propylenoxid-Ethylenoxid-Kondensationsprodukte, Alkylpolyglykolether, Sorbitanfettsäureester, Polyoxethylensorbitanfettsäureester oder Polyoxethylensorbitester.

Stäubemittel werden durch Vermahlen des Wirkstoffes mit fein verteilten, festen Stoffen, z. B. Talkum, natürlichen Tonen wie Kaolin, Bentonit, Pyrophillit oder Diatomeenerde erhalten.

Granulate können entweder durch Verdüsen des Wirkstoffes auf adsorptionsfähiges, granuliertes Inertmaterial hergestellt werden oder durch Aufbringen von Wirkstoffkonzentraten mittels Bindemitteln, z. B. Polyvinylalkohol, polyacrylsaurem Natrium oder auch Mineralölen auf die Oberfläche von Trägerstoffen wie Sand, Kaolinit oder von granuliertem Inertmaterial. Auch können geeignete Wirkstoffe in der für die Herstellung von Düngemittelgranulaten üblichen Weise — gewünschtenfalls in Mischung mit Düngemitteln, granuliert werden.

In Spritzpulvern beträgt die Wirkstoffkonzentration z. B. etwa 10–90 Gew.-%, der Rest zu 100 Gew.-% besteht aus üblichen Formulierungsbestandteilen. Bei emulgierbaren Konzentraten kann die Wirkstoffkonzentration etwa 10–80 Gew.-% an Wirkstoff, bei versprühbaren Lösungen etwa 1–20 Gew.-% betragen. Bei Granulaten hängt der Wirkstoffgehalt zum Teil davon ab, ob die wirksame Verbindung flüssig oder fest vorliegt und welche Granulierhilfsmittel, Füllstoffe usw. verwendet werden.

Daneben enthalten die genannten Wirkstoffformulierungen gegebenenfalls die jeweils üblichen Haft-, Netz-, Dispergier-, Emulgier-, Penetrations-, Lösungsmittel, Füll- oder Trägerstoffe.

Zur Anwendung werden die in handelsüblicher Form vorliegenden Konzentrate gegebenenfalls in üblicher Weise verdünnt, z. B. bei Spritzpulvern, emulgierbaren Konzentraten, Dispersionen und teilweise auch bei Mikrogranulaten mittels Wasser. Staubbörmige und granuliert Zubereitungen sowie versprühbare Lösungen werden vor der Anwendung üblicherweise nicht mehr mit weiteren inerten Stoffen verdünnt.

Auch Mischungen oder Mischformulierungen mit anderen Wirkstoffen, wie z. B. Insektiziden, Akariziden, Herbiziden, Düngemitteln, Wachstumsregulatoren oder weiteren Fungiziden sind gegebenenfalls möglich, wobei u. U. auch synergistische Wirkungssteigerungen erzielt werden können.

Im folgenden seien einige Formulierungsbeispiele angeführt:

Ein Stäubemittel wird erhalten, indem man 10 Gewichtsteile Wirkstoff und 90 Gewichtsteile Talkum als Inertstoff mischt und in einer Schlagmühle zerkleinert.

Ein in Wasser leicht dispergierbares, benetzbares Pulver wird erhalten, indem man 25 Gewichtsteile Wirkstoff, 65 Gewichtsteile kaolinhaltigen Quarz als Inertstoff, 10 Gewichtsteile ligninsulfonsaures Kalium und 1 Gewichtsteil oleoymethyltaurinsaures Natrium als Netz- und Dispergiermittel mischt und in einer Stütmühle mahlt.

Ein in Wasser leicht dispergierbares Dispersionskonzentrat stellt man her, indem man 20 Gewichtsteile Wirkstoff mit 6 Gewichtsteilen Alkylphenolpolyglykolether (Triton X 207), 3 Gewichtsteilen Isotridecanolpolyglykolether (8 AeO) und 71 Gewichtsteilen paraffinischem Mineralöl (Siedebereich z. B. ca. 255 bis über 377°C) mischt und in einer Reibkugelmühle auf eine Feinheit von unter 5 Mikron vermahlt.

Ein emulgierbares Konzentrat läßt sich herstellen aus 15 Gewichtsteilen Wirkstoff, 75 Gewichtsteilen Cyclohexanon als Lösungsmittel und 10 Gewichtsteilen oxethyliertem Nonylphenol (10 AeO) als Emulgator.

Als Beispiel für die Hemmung der pathogenen Phase dimorpher Hefezellen werden Ergebnisse eines in-vitro-Enzymtests angeführt, in welchen die prozentuale Hemmung freigesetzter Exoenzyme, insbesondere freigesetzter Lysophospholipase (Phospholipase B), als Maß für die Wirksamkeit bestimmt wird.

Zur Feststellung der Enzymhemmung wurde eine Suspension von *Candida albicans* Blastokonidien (Stamm 200/175), wobei die Keimdichte photometrisch auf eine Extinktion von 0,5 (500 nm) eingestellt war, mit Präparatelösung bzw. zur Kontrolle mit Lösungsmittellösung vermischt, und zwar

- a) 100 µl Präparatelösung (Suspension) + 900 µl Keimsuspension
- b) 100 µl Lösungsmittel + 900 µl Keimsuspension

Jeweils 5 µl der 30 min bei 21°C inkubierten Blastokonidiensuspension wurden auf eine Agarplatte (Sabouraud Agar mit Zusatz von 8% Eigelb, 1 M NaCl, 5 mN CaCl₂) aufgetropft.

Die so beimpfte Platte wurde 3 Tage bei 37°C bebrütet.

Die Auswertung erfolgte derart, daß

1. der Durchmesser (mm) der *Candida albicans*-Kolonie (behandelt und unbehandelt) sowie
2. der Gesamtdurchmesser von Kolonie und Trübungshof, welcher durch Exoenzyme verursacht wurde (behandelt und unbehandelt) bestimmt wurde.

Aus der Bestimmung des Quotienten von Präparate- und Kontrollgruppe ergab sich ein Wert, der als Maß für die Enzymaktivität anzusehen war.

Wie aus Tabelle 1 ersichtlich, hemmen die erfindungsgemäß verwendeten Verbindungen die freigesetzten Exoenzyme wesentlich stärker als Propanolol

Propranolol wird in der Literatur (Pappu A. S. et al. in Biochem. Pharmacol. 34, 521—24, 1985) als wirksamste Substanz beschrieben, die gegenüber Phospholipase aus Leberzellen in einem entsprechenden in-vitro-Test Hemmwirkung zeigte.

Der Stand der Technik wird durch die erfindungsgemäß verwendeten Verbindungen I überraschenderweise deutlich übertroffen.

5

10

15

20

25

30

35

40

45

50

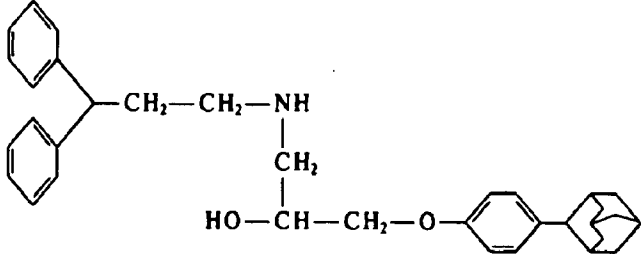
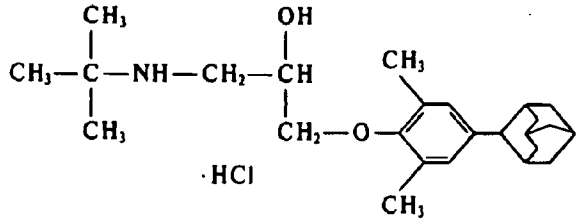
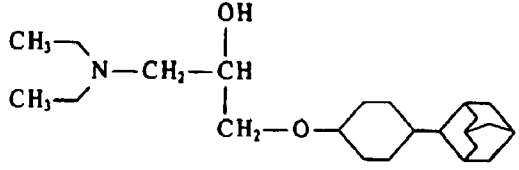
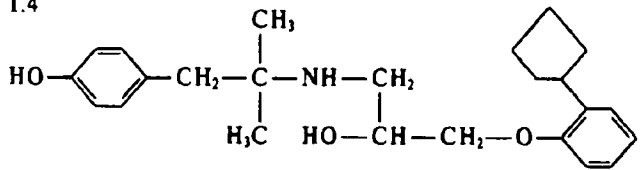
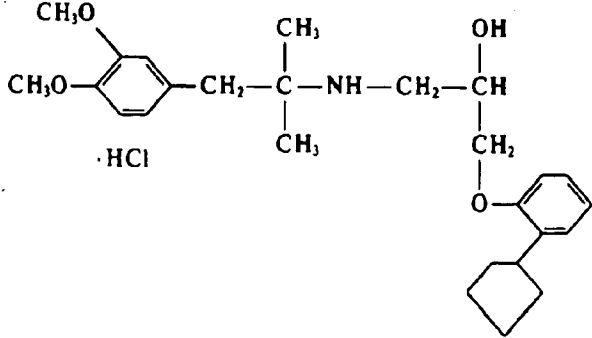
55

60

65

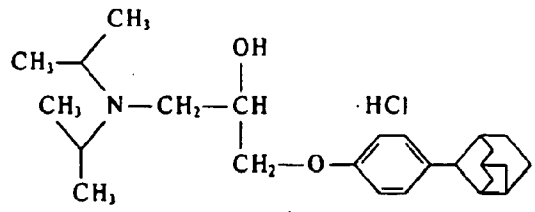
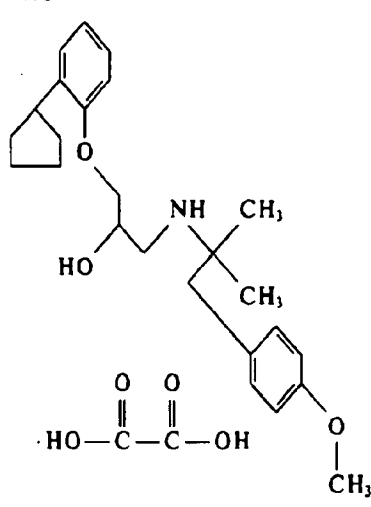
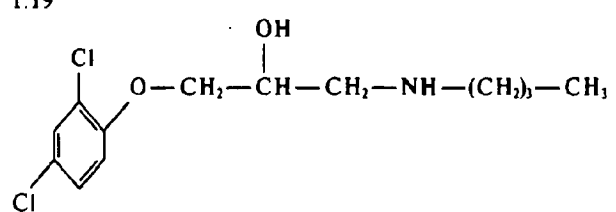
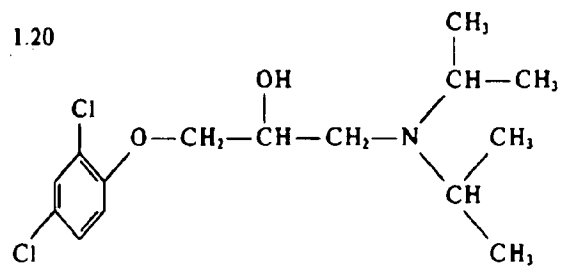
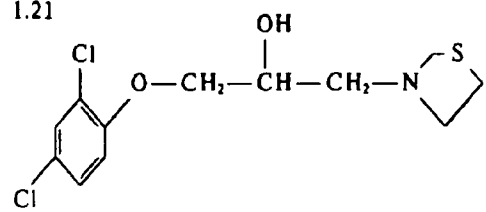
Tabelle 1

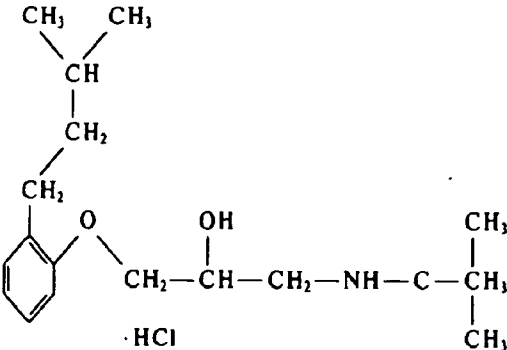
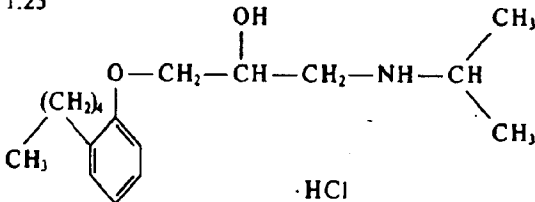
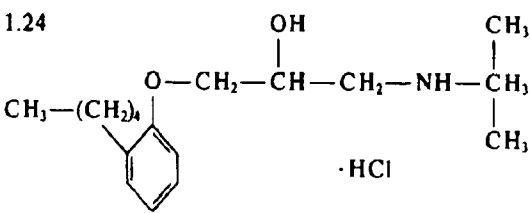
Prozentuale Hemmung der freigesetzten Exoenzyme von *Candida albicans* in vitro

Präparat	Konzentration ($\mu\text{m/ml}$)	% Hemmung der Phospholipase
<p>1.1</p> 	5	62,5
<p>1.2</p>  <p>$\cdot \text{HCl}$</p>	5	50
<p>1.3</p> 	10	42,8
<p>1.4</p>  <p>$\cdot \text{COOH}-\text{COOH}$</p>	50	100
<p>1.5</p>  <p>$\cdot \text{HCl}$</p>	50	50

Präparat	Konzentration ($\mu\text{m/ml}$)	% Hemmung der Phospholipase	
1.6			5
<chem>COc1ccc(cc1)CC(C)(C)NC(CO)COc2ccc(cc2)-c3ccccc3</chem> $\cdot \text{HCl}$	10	87,5	10
1.7			15
<chem>CC(C)CNC(CO)COc1ccc(cc1)-C23CC4CC5C2(C1CC4)C3(C5)C</chem> $\cdot \text{HCl}$	10	50	20
			25
1.8			30
<chem>CC(C)CNC(CO)COc1ccc(cc1)-C23CC4CC5C2(C1CC4)C3(C5)C</chem> $\cdot \text{HCl}$	50 10	75 25	35
1.9			40
<chem>CC(C)CNC(CO)COc1ccc(cc1)-C23CC4CC5C2(C1CC4)C3(C5)C</chem> $\cdot \text{HCl}$	10	75	45
1.10			50
<chem>CC(C)CC(C)CNC(CO)COc1ccc(cc1)-C23CC4CC5C2(C1CC4)C3(C5)C</chem> $\cdot \text{HCl}$	10	75	55
			60
			65

Präparat	Konzentration ($\mu\text{m/ml}$)	% Hemmung der Phospholipase
5		
1.11		
10		
15		
<chem>CC(C)CNCC(O)CCOC1=C(C)C(=C(C)C)C2=CC1C2</chem> $\cdot \text{HCl}$	50	40
1.12		
20		
25		
<chem>Clc1ccc(Cl)cc1OCC(O)CCNCc2ccc(Cl)c(Cl)c2</chem>	100 50	100 100
1.13		
30		
35		
<chem>COc1ccc(cc1)CC(C)NCC(O)CCOc2ccccc2C</chem>	50 10	100 30
1.14		
40		
45		
<chem>c1ccccc1CCCNCC(O)CCOc2ccc(cc2)Cc3ccccc3</chem> $\cdot \text{HCl}$	50 10	100 33
1.15		
50		
<chem>c1ccccc1CCCNCC(C)COc2ccc(cc2)Cc3ccccc3</chem> $\cdot \text{HCl}$	50 10	86 29
1.16		
55		
60		
<chem>CC(C)(C)c1ccc(OCC(O)CNc2ccccc2)cc1</chem> $\cdot \text{HCl}$	100 50 10	100 100 50
65		

Präparat	Konzentration ($\mu\text{m/ml}$)	% Hemmung der Phospholipase	
1.17			5
	100 50 10	100 100 92,9	10
1.18			15
	50 10	91 14,3	20
1.19			25
	100 50	100 87,5	30
1.20			35
	100 50	100 30	40
1.21			45
	100 50 10	100 44,4 25	50
			55
			60
			65

Präparat	Konzentration ($\mu\text{m}/\text{ml}$)	% Hemmung der Phospholipase
1.22		
	100 50	100 100
1.23		
	100 50	100 100
1.24		
	100 50	100 100
Propranolol	100	30

Als Beispiele für die systemische in vivo-Wirksamkeit der Verbindungen dient die systemische *Candida albicans* Infektion bei der Maus.

Ziel dieser Methode ist es, den Effekt von Präparaten auf eine systemische *Candida albicans* Infektion zu ermitteln. Die Infektion führt innerhalb von 2-4 Tagen zum Tod der Tiere.

Beschreibung der Methode: Albino Mäuse (NMRI, Männchen, 15–20 g Körpergewicht) werden intravenös mit *Candida albicans* Hefezellen infiziert (Stamm 200/175), die frisch auf Malzagar vorkultiviert wurden und in physiologischer Kochsalzlösung suspendiert wurden. Die Infektionsdosis, die in dem angegebenen Zeitrahmen zur Lethalität führt, wurde photometrisch eingestellt und enthielt eine Million Hefezellen pro Maus.

Die zu prüfenden Verbindungen werden entweder alleine oder in Kombination mit einem Standardantimykotikum verabreicht. Im durchgeführten Test wurde ein Kombinationspräparat verwendet, wobei als Standardantimykotikum Fluconazol (Fa. Pfizer) diente. Applikationswege sind je nach Substanzgruppe unterschiedlich, wobei der oralen Applikation der Vorzug gegeben wird. Die Mäuse werden 4 Wochen beobachtet, die Mortalität wird täglich registriert, und die Überlebenszeit der einzelnen Gruppen werden gemittelt und untereinander verglichen. Gruppengröße beträgt durchschnittlich 10 Tiere.

Der Vergleich der Mittelwerte geschieht mit dem Students T Test.

Wie Tabelle 2 zeigt, verlängert sich beispielsweise bei Gabe von Verbindung 1,16 ($14 \times 50 \text{ mg/kg p. o. } 1 \times \text{täglich}$) die Überlebenszeit von mit *Candida* infizierten Mäusen um 65% (Die Überlebenszeit der mittels Fluconazol-Monotherapie behandelten Tiere wurde als 100 definiert, worauf sich für die Kombinationstherapie 165 ergaben).

Tabelle 2

Überlebenszeiten von mit *Candida* infizierten Mäusen bei Kombinationstherapie mit Fluconazol

Verbindung	Überlebenszeit (bez. auf Fluconazol = 100%)	5
Fluconazol	100%	
Fluconazol + Verbd. 1,7	127%	
Fluconazol + Verbd. 1,9	131%	10
Fluconazol + Verbd. 1,10	149%	
Fluconazol + Verbd. 1,16	165%	

Dosierungen:

Fluconazol jeweils 8 x p. o. 50 mg/kg/Tag

ß-Hydroxy-ethylamin jeweils 14 x p. o. 50 mg/kg/Tag

Die pilzabtötende, antimykotische Wirksamkeit der Verbindungen wurde an einigen Beispielen (s. Tabelle 3) anhand der prozentualen Abtötung von *Trichophyton mentagrophytes* in vitro verifiziert (Standardpräparat Rilopirox als Vergleichssubstanz).

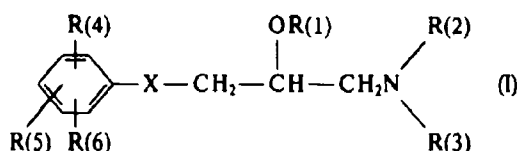
Tabelle 3

Verbindung	µg/ml 80	40	20	10	5	2,5	25
1,1	100	100	99,8	99,4	98,7	80,8	
1,2	100	100	100	100	98,7	92,3	30
1,3	100	100	99,8	98,9	74,9	52,7	
1,17	100	100	100	99,8	87,1	73,4	
1,18	100	100	100	100	95,7	79,3	
Rilopirox	100	100	100	100	96,2	94,1	

(Werte in %-Abtötung von *Trichophyton mentagrophytes* nach 14 h in aqua dest.)

Patentansprüche

1. Verwendung einer Verbindung der Formel I



und ihrer Salze mit pharmazeutisch akzeptablen Säuren zur Herstellung eines Medikaments zum Behandeln von Pilzkrankungen,

in welchen Verbindungen bedeuten:

R(1) H, (C₁-C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂-C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Benzyl (unsubstituiert oder ein- oder mehrfach substituiert durch F, Cl, Br, CF₃, (C₁-C₄)-Alkyl (geradkettig oder verzweigt), OCH₃, O-Phenyl oder Phenyl)

R(2) H, (C₁-C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂-C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃-C₁₀)-Cycloalkyl, Phenyl-(C₁-C₆)-Alkyl (geradkettig oder verzweigt), Phenyl-(C₂-C₆)-Alkenyl (geradkettig oder verzweigt, ein- oder zweifach ungesättigt), Diphenyl-(C₁-C₆)-Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert oder ein- oder mehrfach substituiert ist durch Substituenten aus der Gruppe F, Cl, Br, (C₁-C₄)-Alkyl (geradkettig oder verzweigt), (C₃-C₈)-Cycloalkyl, OH, SH, (C₁-C₁₀)-Akoxy (geradkettig oder verzweigt), Phenyl, Benzyl, Phenethyl, Thiophenyl, C_nF_{2n+1} mit n = 1-6,

R(3) wie R(2) definiert ist, wobei R(2) und R(3) jeweils gleiche oder verschiedene Bedeutung aufweisen, oder

R(2) mit R(3) eine Kette -(CH₂)_m- mit m gleich 4-6 bildet, in welcher eine CH₂-Gruppe durch Sauerstoff, Schwefel oder Stickstoff ersetzt sein kann, wobei N als weiteren Bindungspartner ein H-Atom, eine CH₃, Phenyl-, Benzyl oder Phenethylgruppe trägt, und

R(4) H, (C₁-C₁₅)-Alkyl (geradkettig oder verzweigt), (C₂-C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃-C₂₀)-Cycloalkyl [mono-, bi- oder multicyclisch, unsubstituiert oder ein-

oder zweifach mit (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt), C_nF_{2n+1} (mit n gleich 1–4), F, Cl, Br, OH substituiert), Y-(C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), Y-(C₂–C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y-(C₃–C₂₀)-Cycloalkyl (mono-, bi- oder multicyclisch, unsubstituiert oder wie oben angegeben substituiert), Phenyl, Y-Phenyl, Phenyl-(C₁–C₂)-Alkyl, Biphenyl, F, Cl, Br, I, C_nF_{2n+1} (mit n gleich 1–8), CCl₃, YH, Naphthyl, CN, NO₂, mit Y gleich Sauerstoff oder Schwefel

und

R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind,

und

R(4) mit R(5), für den Fall, daß die Substituenten an benachbarten Positionen am Phenylring gebunden sind, gemeinsam eine (CH₂)_p-Kette mit p gleich 3 oder 4 bilden können,

und

R(6) H, (C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y-(C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), Y-(C₂–C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Phenyl, Y-Phenyl, Benzyl, Biphenyl, F, Cl, Br, I, C_nF_{2n+1} (mit n gleich 1–8), CCl₃, Naphthyl, YH

Y = Sauerstoff, Schwefel

X = Sauerstoff, Schwefel, SO, SO₂,

und ihre Salze mit pharmazeutisch akzeptablen Säuren.

2. Verwendung von Verbindungen I nach Anspruch 1, in denen bedeuten:

R(1) H, (C₁–C₈)-Alkyl (geradkettig oder verzweigt), (C₃–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Benzyl (unsubstituiert oder einfach oder zweifach substituiert durch F, Cl, CF₃, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), OCH₃,

R(2) H, (C₁–C₈)-Alkyl (geradkettig oder verzweigt), (C₃–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Phenyl-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Diphenyl-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert ist oder ein- oder zweifach substituiert ist durch Substituenten aus der Gruppe OH, F, Cl, Br, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt), Phenyl, Benzyl, Phenethyl,

R(3) wie R(2) definiert ist, wobei R(2) und R(3) jeweils gleiche oder verschiedene Bedeutung aufweisen,

oder

R(2) mit R(3) eine Kette (CH₂)_m mit m gleich 4–6 bildet, in welcher eine CH₂-Gruppe durch ein Sauerstoff oder Stickstoff-Atom ersetzt sein kann, wobei N als weiteren Bindungspartner ein H-Atom, eine CH₃, Phenyl-, Benzyl oder Phenethylgruppe trägt,

und

R(4) H, (C₁–C₁₅)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₅)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch, unsubstituiert oder einfach mit (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt), substituiert), Y-(C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y-(C₃–C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch, unsubstituiert oder wie oben angegeben substituiert), Phenyl, Y-Phenyl, Phenyl-(C₁–C₂)-Alkyl, Biphenyl, F, Cl, C_nF_{2n+1} (mit n gleich 1–4), CCl₃, Naphthyl, CN, mit Y gleich Sauerstoff oder Schwefel

und

R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind,

und

R(4) mit R(5), für den Fall, daß die Substituenten an benachbarten Positionen am Phenylring gebunden sind, gemeinsam eine (CH₂)_p-Kette mit p = 3 oder 4 bilden können,

und

R(6) H, (C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Phenyl, Benzyl, Biphenyl, F, Cl, Br, C_nF_{2n+1}

Y = Sauerstoff, Schwefel

X = Sauerstoff, Schwefel.

3. Verwendung von Verbindungen I nach Anspruch 1, in denen bedeuten:

R(1) H, (C₁–C₈)-Alkyl (geradkettig oder verzweigt), Benzyl (unsubstituiert oder ein- oder zweifach substituiert durch F, Cl, CF₃, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), OCH₃,

R(2) H, (C₁–C₈)-Alkyl (geradkettig oder verzweigt), (C₃–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder zweifach ungesättigt), Phenyl-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Diphenyl-(C₁–C₆)-Alkyl (geradkettig oder verzweigt), Phenyl, wobei das Phenylsystem unsubstituiert oder ein- oder zweifach substituiert ist durch Substituenten aus der Gruppe OH, F, Cl, Br, (C₁–C₄)-Alkyl (geradkettig oder verzweigt), (C₁–C₄)-Alkoxy (geradkettig oder verzweigt), Phenyl, Benzyl,

R(3) H

oder

R(2) gemeinsam mit R(3) eine Kette –(CH₂)_m– mit m gleich 4–5 bildet, in welcher eine CH₂-Gruppe durch ein Sauerstoff- oder N-Atom ersetzt sein kann, wobei N als weiteren Bindungspartner ein H-Atom, eine CH₃, Phenyl-, Benzyl oder Phenethylgruppe trägt,

und

R(4) H, (C₁–C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂–C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃–C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch (wie z. B. Norbornyl, Ada-

mantyl, Decahydronaphthalinyl, Y-(C₁-C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₂-C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), Y-(C₃-C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch), Phenyl, Y-Phenyl, Benzyl, Bisphenyl, F, Cl, C_nF_{2n+1} (mit n gleich 1-4), CCl₃, Naphthyl, CN, mit Y gleich Sauerstoff oder Schwefel,

und

R(5) wie R(4) definiert, wobei R(4) und R(5) gleich oder verschieden sind,

und

R(6) H, (C₁-C₄)-Alkyl (geradkettig oder verzweigt), Y-(C₁-C₄)-Alkyl (geradkettig oder verzweigt), F, Cl, CF₃

Y = Sauerstoff, Schwefel

X = Sauerstoff.

4. Verwendung von Verbindungen I nach Anspruch 1, bei denen die Substituenten bedeuten

R(1) H, Benzyl,

R(2) H, (C₁-C₃)-Alkyl (geradkettig oder verzweigt), Phenyl-(C₁-C₄)-Alkyl (geradkettig oder verzweigt), wobei das Phenylsystem unsubstituiert oder einfach substituiert ist durch F, Cl, (C₁-C₄)-Alkyl (geradkettig oder verzweigt), (C₁-C₄)-Alkoxy (geradkettig oder verzweigt),

R(3) H,

und

R(4) H, (C₁-C₁₀)-Alkyl (geradkettig oder verzweigt), (C₂-C₁₀)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃-C₁₅)-Cycloalkyl [mono-, bi- oder multicyclisch] Y-(C₁-C₁₀)-Alkyl (geradkettig oder verzweigt), Y-(C₃-C₁₅)-Cycloalkyl (mono-, bi- oder multicyclisch), Phenyl, Y-Phenyl, Benzyl, Biphenyl, F, Cl, C_nF_{2n+1} (mit n = 1-4), mit Y gleich Sauerstoff

und

R(5) H, (C₁-C₆)-Alkyl (geradkettig oder verzweigt), (C₂-C₆)-Alkenyl (geradkettig oder verzweigt, ein- oder mehrfach ungesättigt), (C₃-C₆)-Cycloalkyl Y-(C₁-C₆)-Alkyl (geradkettig oder verzweigt), Y-(C₃-C₆)-Cycloalkyl, Phenyl, Y-Phenyl, Benzyl, F, Cl, CF₃

mit Y gleich Sauerstoff und X gleich Sauerstoff,

R(6) H

und ihre Salze mit pharmazeutisch akzeptablen Säuren.

5. Verwendung einer Verbindung I nach Anspruch 1 zur Prophylaxe von Pilzkrankungen.

2003-835650/78 B03 (B02) WARN 2002.03.28
 WARNER LAMBERT CO LLC *EP 1348701-A1
 2002.03.28 2002-290788(+2002EP-290788) (2003.10.01) C07D
 277/42, A61K 31/426, C07D 417/04, A61K 31/427

New (2,4-disubstituted-thiazol-5-yl)amine compounds useful for treating diseases e.g. osteoarthritis, multiple sclerosis, osteoporosis, asthma, cancer and graft rejection (Eng)

C2003-235032 R(AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI
 LT LU LV MC MK NL PT RO SE SI TR)

Addnl. Data: VERGNE F, BERNARDELLI P, LORTHOIS E, DUCROT P

NOVELTY

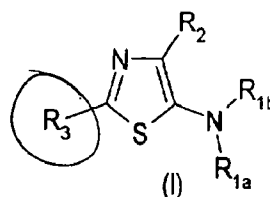
(2,4-Disubstituted-thiazol-5-yl)amine compounds (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.

DETAILED DESCRIPTION

(2,4-Disubstituted-thiazol-5-yl)amine compounds of formula (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.

B(6-H, 7-F1, 14-C1, 14-C3, 14-C9A, 14-D7A, 14-E10, 14-G1B, 14-G2A, 14-G2C, 14-G2D, 14-H1, 14-J1, 14-K1, 14-N1, 14-N4, 14-N11, 14-S1) .11

R_3 -COOH
 reactant



R_{1a} = H or (aryl)1-6C alkyl;

R_{1b} = (hetero)cycloalkyl, or (hetero)aryl (all optionally substituted by halo, trifluoromethyl, nitro, cyano, oxo, -NR₄R₅, -CO₂R₄, -CONR₄R₅, -OR₄, -S(O)_nR₄, -S(O)_nR₄R₅, tetrazolyl or 1-6C alkyl (optionally mono- or tri-substituted by -OR₄, -NR₄R₅ or -CO₂R₄);

n and m = 0 - 2;

R₄ and R₅ = H or -X₁R₆;

X₁ and X₂ = single bond or 1-6C alkylene;

EP 1348701-A+

R_6 = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl;
 R_2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, aryl or cycloalkyl;
 R_3 = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halogen, nitro, cyano, trifluoromethyl, oxo, 1-6C alkyl, -OR₆, -NR₆R₇, -COR₆, -CO₂R₆, -CONHOH, -CONR₆R₇, -S(O)_mR₆, -S(O)_m-NR₆R₇, -NR₆COR₇, -NR₆SO₂R₇, -N(SO₂R₇)₂, -NR₆-CO-NR₇R₈ or tetrazolyl;

R_6 and R_7 = H or -X₂R₆;

R_b = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl (all optionally mono- or tri-substituted by OH, 1-6C alkoxy, 1-6C alkyl, amino, mono-1-6C alkylamino, di-1-6C alkylamino, carboxy, 1-6C alkoxycarbonyl or benzyl; and

R_8 = H or 1-6C alkyl.

The aryl is an aromatic monocyclic or bicyclic system containing 5-10C; in the bicyclic ring system, one of the rings is aromatic and the other ring is optionally aromatic or partially hydrogenated and when the second ring is partially hydrogenated, then the ring is optionally mono- or di-substituted by oxo. The heteroaryl is the aryl group in which 1 - 4 carbon atoms are replaced by 1 - 4 heteroatoms selected from O, S and N. The cycloalkyl is a monocyclic or polycyclic system containing 3 - 10C and is saturated or partially unsaturated but without aromatic character and in the polycyclic system, each cycle could be

fused together or formed a link. The heterocycloalkyl is the cycloalkyl group in which 1 - 4 carbon atoms are replaced by 1 - 4 heteroatoms selected from O, S or N.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY

Immunosuppressive; Antiinflammatory; Respiratory-Gen.; CNS-Gen.; Antiallergic; Gastrointestinal-Gen.; Analgesic; Osteopathic; Neuroprotective; Antiasthmatic; Cytostatic; Anti-HIV; Antiarthritic.

MECHANISM OF ACTION

Phosphodiesterase-7 (PDE-7) inhibitor.

(I) were tested for inhibition of cyclic nucleotide phosphodiesterase 7, as given in W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol.10:69 - 92, ed.G.Brooker et al. Raven Press, NY. They showed IC₅₀ value of 0.02 - 100 micro M. No results for specific compounds are given.

USE

For the treatment of a disease including T-cell related disease, autoimmune disease, inflammatory disease, respiratory disease, CNS

EP 1348701-A+/1

2003-835650/78

disease, allergic diseases, endocrine or exocrine pancreas disease, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection (claimed).

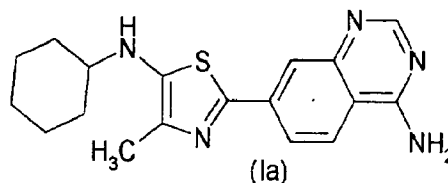
ADVANTAGE

The compounds are active at very low concentrations.

SPECIFIC COMPOUNDS

4 Compounds (I) are specifically claimed, e.g. 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4-amine (Ia).

BEST AVAILABLE COPY



ADMINISTRATION

The compounds, in a dosage of 1 mg - 1 g per day, can be administered orally, parenterally (including intravenously, intramuscularly or subcutaneously), per- or trans-cutaneously, intravaginally, rectally, nasally, perlingually, buccally, ocularly or by respiratory route.

EXAMPLE

To a solution of 4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid in tetrahydrofuran (THF) was added 1,1'-carbonyldiimidazole (1.2

EP 1348701-A+/2

(con't)

equivalents) and the mixture was stirred for 30 minutes. The (S)-L-alanine tert-butyl ester was added and the mixture was stirred for 24 hours. The solvent was removed and the residue was worked up to obtain tert-butyl(2S)-2-[[4-oxo-3,4-dihydroquinazolin-7-yl]carbonyl]amino]propanoate (A).

(A) was added to a solution of 5% trifluoroacetic acid in dichloromethane and the mixture was stirred for 3 hours, followed by a work-up to obtain (2S)-2-[[4-oxo-3,4-dihydroquinazolin-7-yl]carbonyl]amino]propanoic acid (A1).

To a solution of (A1) in THF, 1,1'-carbonyldiimidazole (1.2 equivalents) was added and the mixture was stirred for 30 minutes. Then the cyclohexylamine was added and the mixture was stirred for 24 hours, followed by a work-up to obtain N-[(1S)-2-(cyclohexylamino)-1-methyl-2-oxoethyl]-4-oxo-3,4-dihydroquinazoline-7-carboxamide (A2).

To a solution of (A2) in pyridine was added Lawesson's reagent and the mixture was heated to 100°C for 6 hours. After cooling to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture and the product was worked up to obtain 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4(3H)thione (A3).

To a stirring solution of (A3) and potassium carbonate (1.2

equivalents) in methanol was added CH₃I. After 30 minutes, the solvent was removed to obtain N-cyclohexyl-4-methyl-2-[4-(methylthio)quinazolin-7-yl]-1,3-thiazol-5-amine (A4).

A solution of (A4) in saturated butanolic ammonia was sealed in steel bomb and heated at 100°C for 2 days. The solvent was removed and the residue was purified to obtain 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4-amine (1a).

DEFINITIONS

Preferred Definitions:

R_{1a} = H;

R_{1b} = cyclohexyl group (optionally mono-substituted by OH) or phenyl (optionally mono-substituted by tetrazolyl or -CO₂R₄);

R₄ = H or 1-6C alkyl;

R₂ = methyl;

R₃ = quinoxaliny, 1H-quinazolinyl, 3H-quinazolinyl-4-one, 1H-quinazolinyl-2,4-dione (all optionally mono- tri-substituted by halo, 1-6C alkyl, OR₆ or NR₆R₇);

X₂ = single bond;

R_b = 1-6C alkyl (optionally monosubstituted by OH, 1-6C alkoxy, amino, mono-1-6C alkylamino or di-1-6C alkylamino).

EP 1348701-A+/3

2003-835650/78

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (Claimed): Preparation of (I) involves:

- (1) coupling a carboxylic acid of formula R₃-C(=O)OH with an amine of formula ProtO-C(=O)-CHR₂-NH₂ under peptidic coupling conditions to give a coupled product of formula R₃-C(=O)-NH-CH(CO₂Prot)-R₂;
- (2) deprotecting the coupled product by treatment with an acid or base to give a free carboxylic acid compound of formula R₃-C(=O)-NH-CH(CO₂H)-R₂ (V);
- (3) reacting (V) with a primary amine of formula R_{1b}-NH₂ under peptidic coupling conditions in the presence of a coupling agent to give a couple product of formula R₃-C(=O)-NH-CH(R₂)-C(=O)-NH(R_{1b}) (VI);
- (4) treating (VI) with Lawesson's reagent in basic medium to give (I) (in which R_{1a} is H);
- (5) treating (I) (in which R_{1a} is H) with R'_{1a}-L₁ to give(I) (in which R_{1a} is R'_{1a}) optionally under alkaline medium;
- (6) purifying (I) (in which R_{1a} is H or R'_{1a}) by a conventional purifying

technique; and

(7) separating into their respective isomers, followed by converting into their salts with acid or base or into N-oxide.

Prot = protective group of carboxylic acid group;

R'_{1a} = (aryl)1-6C alkyl;

L₁ = leaving group.

(20pp8014DwgNo.0/0)

EP 1348701-A/4

2003-835642/78 B03 (B02) WARN 2002.03.28
 WARNER LAMBERT CO LLC *EP 1348433-A1
 2002.03.28 2002-290787(+2002EP-290787) (2003.10.01) A61K
 31/426, 31/427, A61P 37/00, C07D 277/42, 417/04

New thiazol-2-yl-imine compounds useful as phosphodiesterase-7 inhibitors for treating e.g. osteoarthritis, multiple sclerosis, osteoporosis, asthma, cancer and graft rejection (Eng)

C2003-235024 R(AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI
 LT LU LV MC MK NL PT RO SE SI TR)

Addnl. Data: VERGNE F, BERNARDELLI P, LORTHOIS E, DUCROT F

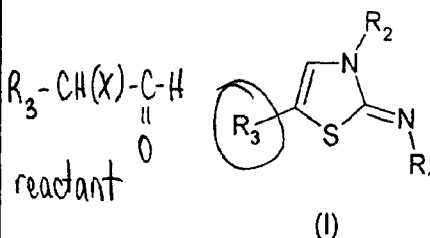
NOVELTY

Thiazol-2-yl-imine compounds (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.

DETAILED DESCRIPTION

Thiazol-2-yl-imine compounds of formula (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new;

B(7-F1, 14-A2B1, 14-C1, 14-C3, 14-C9A, 14-D7A, 14-E10, 14-E10C, 14-G1B, 14-G2A, 14-G2C, 14-G2D, 14-H1, 14-J1, 14-K1, 14-K1A, 14-N4, 14-N13, 14-S1) .11



R₁ = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halogen, trifluoromethyl, nitro, cyano, oxo, -NR₄R₅, -CO₂R₄, -CONR₄R₅, -OR₄, -S(O)_nR₄, -S(O)_nR₄R₅, tetrazolyl or 1-6C alkyl (optionally mono- - tri-substituted by -OR₄, -NR₄R₅ or -CO₂R₄));
 n, m = 0-2;
 R₄, R₅ = H or -X₁R₄;
 R₂ = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, aryl or cycloalkyl;
 X₁, X₂ = single bond or 1-6C alkylene;

EP 1348433-A+

R₆ = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl;
 R₃ = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halo, nitro, cyano, trifluoromethyl, oxo, 1-6C alkyl, -OR₆, -NR₆R₇, -COR₆, -CO₂R₆, -CONHOH, -CONR₆R₇, -S(O)_mR₆, -S(O)_m-NR₆R₇, -NR₆COR₇, -NR₆SO₂R₇, -N(SO₂R₇)₂, -NR₆-CO-NR₇R₈ or tetrazolyl);

R₆, R₇ = H or -X₂R₆;

R₆ = 1-6C alkyl, (hetero)cycloalkyl, or (hetero)aryl (all optionally mono- - tri-substituted by OH, 1-6C alkoxy, 1-6C alkyl, amino, mono-1-6C alkylamino, di-1-6C alkylamino, carboxy, 1-6C alkoxycarbonyl or benzyl);

R₈ = H or 1-6C alkyl.

The aryl is an aromatic monocyclic or bicyclic system containing 5-10C and in the bicyclic ring system, one of the ring is aromatic and the other ring is optionally aromatic or partially hydrogenated and when the second ring is partially hydrogenated, then the ring is optionally mono- or di-substituted by oxo.

The heteroaryl is the aryl group in which 1-4 carbon atoms are replaced by 1-4 heteroatoms selected from O, S or N.

The cycloalkyl is a monocyclic or polycyclic system containing 3-10C and is saturated or partially unsaturated but without aromatic character and in the polycyclic system, each cycle could be fused together or

formed a link.

The heterocycloalkyl is the cycloalkyl group in which 1-4 carbon atoms are replaced by 1-4 heteroatoms selected from O, S and N. An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY

Immunosuppressive; Antiinflammatory; Respiratory-Gen.; CNS-Gen.; Antiallergic; Gastrointestinal-Gen.; Analgesic; Osteopathic; Neuroprotective; Antiasthmatic; Cytostatic; Anti-HIV; Antiarthritic.

MECHANISM OF ACTION

Phosphodiesterase-7 (PDE-7) inhibitor.

The compounds (I) were tested to inhibit cyclic nucleotide phosphodiesterase 7 as given in W.J.Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol.10:69 - 92, ed. G.Brooker et al. Raven Press, NY and showed IC₅₀ value of 0.02-100 micro M. No results for specific compounds are given.

USE

(I) Are used for the treatment of a disease (e.g. T-cell related disease, autoimmune disease, inflammatory disease, respiratory

EP 1348433-A+/1

2003-835642/78

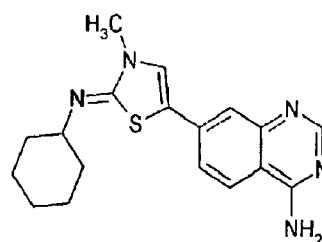
disease, CNS disease, allergic diseases, endocrine or exocrine pancreas disease, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection (claimed).

ADVANTAGE

The compounds (I) are selective PDE-7 inhibitors and are active at very low concentrations.

SPECIFIC COMPOUNDS

4 Compounds are specifically claimed as (I), i.e. N-{4-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide, N-{4-[(2Z)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide, 7-[(2Z)-2-(cyclohexylamino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazoline-4-amine (Ia) and 7-[(2Z)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazoline-4-amine.



(Ia)

ADMINISTRATION

(I) Are administered orally, parenterally (including intravenously, intramuscularly or subcutaneously), per- or trans-cutaneously, intravaginally, rectally, nasally, perlingually, buccally, ocularly or by respiratory route, at a dosage of 1 mg - 1 g per day.

EXAMPLE

EP 1348433-A+/2

(con't)

A solution of bromo-(4-oxo-3,4-dihydro-quinazolin-7-yl)acetaldehyde and N-cyclohexylthiourea in dimethylformamide was heated at 70 °C for 5-12 hours. The mixture was quenched with 10% dimethylamine in ethanol and the solvent was removed, the crude was purified to obtain 7-[2-(cyclohexylamino)-1,3-thiazol-5-yl]quinazolin-4(3H)-one (A).

To a solution of (A) in anhydrous dioxane, methyltrifluoromethane sulfonate (1.1 equivalents) was added. The resulting mixture was stirred for 24 hours. Triethylamine (2 equivalents) was added, then the mixture was concentrated. The residue was purified to obtain 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4(3H)-one (A1).

A mixture of (A1), thionyl chloride and dimethylformamide, in toluene was refluxed for 3 hours before distillation of solvents under reduced pressure. The residue was diluted in dichloromethane and then neutralized with triethylamine, followed by a work-up to obtain N-(2Z)-5-(4-chloroquinazolin-7-yl)-3-methyl-1,3-thiazol-2(3H)-ylidene]-N-cyclohexylamine (A2).

A solution of (A2) in a 2 N solution of ammonia (NH₃) in isopropanol was stirred for 6 hours at 60 °C.

The mixture was then concentrated. To this residue a solution of sodium hydroxide (NaOH) (0.1 N) was added and then worked up to

obtain 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4-amine (1a).

DEFINITIONS

Preferred Definitions:

R₁ = cyclohexyl group (optionally mono-substituted by OH) or phenyl (optionally mono-substituted by tetrazolyl or -CO₂R₄);

R₄ = H or 1-6C alkyl;

R₂ = methyl;

R₃ = quinoxaliny, 1H-quinazoliny, 3H-quinazoliny-4-one or 1H-quinazoliny-2,4-dione (all optionally mono- tri-substituted by halo, 1-6C alkyl, OR₆ or NR₆R₇);

X₂ = single bond;

R₆ = 1-6C alkyl (optionally monosubstituted by OH, 1-6C alkoxy, amino, mono-1-6C alkylamino or di-1-6C alkylamino).

TECHNOLOGY FOCUS

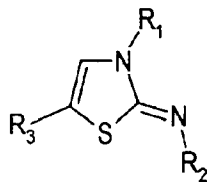
Organic Chemistry - Preparation (claimed): Preparation of (I) involves:

(1) reacting an α-haloacetate of formula R₃-CH(X)-C(=O)-H (II) with a thiourea of formula R₂-NH-C(=S)-NH-R₁ (III) in the presence of an inert solvent under heating condition to form a mixture of

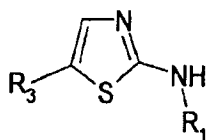
EP 1348433-A+/3

2003-835642/78

- formula (I) and (IV), followed by separation of (I) from the mixture, or reacting (II) with thiourea of compound of formula H₂N-C(=S)-NH-R₁ (V) to give thiazole derivative of formula (VI);
- (2) condensing (VI) with R₂-L₁ (VII) to give (I);
 - (3) purifying (I) by a conventional purifying technique; and
 - (4) separating into their respective isomers, followed by converting into their salts with acid or base or into N-oxide.



(IV)



(VI)

X = halogen;

L¹ = leaving group.

All other definitions are as above.

(19pp8014DwgNo.0/0)

EP 1348433-A/4

2003-689639/65 B02 ASTR 2002.02.13
 ASTRAZENECA AB *WO 2003068754-A1
 2002.10.22 2002-003122(+2002SE-000450) (2003.08.21) C07D
 231/56, A61K 31/341, 31/4025, 31/416, 31/4427, C07D 403/04, 405/04,
 401/12, A61P 9/00, 25/00, 35/00

New indazole derivatives are c-Jun terminal kinase inhibitors used for treating e.g. Alzheimer's disease and cognitive disorders and Parkinson's disease (Eng)

C2003-189122 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
 CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
 MN MW MX MZ NO NZ OM PH PL PT RO RU SC
 SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ
 VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE
 DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
 LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR
 TZ UG ZM ZW)

Addnl. Data: MALMSTROEM J, SWAHN B
 2003.02.11 2003WO-SE00227, 2002.10.22 2002SE-003122

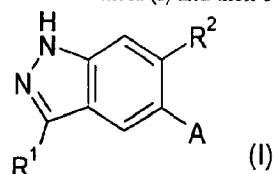
NOVELTY

Indazole derivatives (I) are new.

B(6-D5, 14-C1, 14-C3, 14-C4, 14-C9, 14-D6, 14-G1B,
 14-H1, 14-J1A3, 14-J1A4, 14-N16) .7

DETAILED DESCRIPTION

Indazole derivatives of formula (I) and their salts are new.



R¹ = aryl or heteroaryl (both optionally substituted by at least one R³, OR³, OCOR³, COOR³, COR³, CONR³R⁴, NHCOR³, NR³R⁴, NHSO₂R³, SO₂R³, SO₂NR³R⁴, SR³, CN, halo or NO₂);
 R² = NO₂, NH₂, NR⁵R⁶ or NR⁶R⁷;
 R³, R⁴ = 1-6C alkyl, 2-6C alkenyl, 3-8C cycloalkyl-(0-6C)alkyl, 1-6C fluoroalkyl, heterocycle-(0-6C)alkyl or heteroaryl-(0-6C)alkyl (all optionally substituted by at least one B') or H, or

WO 2003068754-A+

R³ + R⁴ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B');
 B' = T, COR¹⁰ or oxo;
 T = R¹⁰, COOR¹⁰, NHCOR¹⁰, NR¹⁰R¹¹, CONR¹⁰R¹¹, OR¹⁰, SO₂NR¹⁰R¹¹, CN or halo;

R⁵ = phenyl or heteroaryl (both optionally substituted by at least one T, OCOR¹⁰, NHCOR¹⁰, NR¹⁰R¹¹, CONR¹⁰R¹¹, OR¹⁰, SO₂NR¹⁰R¹¹, CN or halo);

R⁶ = H, 1-6C alkyl, heterocycle(0-6C)alkyl or hydroxy(1-6C)alkyl;

R⁷ = 1-6C alkyl, 3-8C cycloalkyl(0-6C)alkyl, 5-8C cycloalkenyl(0-6C)alkyl or R⁵(1-6C)alkyl;

A = H, R⁸, OR⁸, OCOR⁸, COOR⁸, CONR⁸R⁹, NHCOR⁸, NR⁸R⁹, NHCOR⁸, SO₂R⁸, SO₂NR⁸R⁹, SR⁸, CN, halo, heterocycle(0-6C)alkyl or heteroaryl(0-6C)alkyl;

R⁸, R⁹ = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, heterocycle(0-6C)alkyl or heteroaryl(0-6C)alkyl (all optionally substituted by at least one B'), or H, or

R⁸ + R⁹ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B'), and

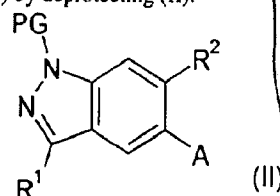
R¹⁰, R¹¹ = H, 1-6C alkyl, 1-6C fluoroalkyl or hydroxy(1-6C)alkyl, or

R¹⁰ + R¹¹ = 5-7 membered heterocyclyl containing 1-4 N, O, or S heteroatoms (optionally substituted by at least one B'), provided that (I) is not 6-amino-3-(4-fluorophenyl)-indazole, 6-amino-

3-phenyl-indazole, 6-nitro-3-phenyl-indazole and 6-nitro-3-(4-nitrophenyl)-indazole, and has no quinazoline in the R³ position.

INDEPENDENT CLAIMS are also included for:

- (1) new intermediate compounds of formula (II), and
- (2) preparation of (I) by deprotecting (II).



R⁵-X
 = reactant

PG = amino protecting group.

ACTIVITY

Neuroprotective; Nootropic; Antiparkinsonian; Anticonvulsant; Anti-HIV; Cytostatic; Antiinflammatory; Antipyretic; Analgesic.

MECHANISM OF ACTION

c-Jun N-terminal kinase (JNK) inhibitor.

WO 2003068754-A+

2003-689639/65

In a scintillation proximity assay (SPA) based on the inhibition of JNK3 catalyzed transfer of the γ-phosphate group of [γ-³²P] adenosine triphosphate (ATP) to biotinylated activating transcription factor (ATF)-2, (I) exhibited K_i values of 0.001-10000 (especially 0.001-300) nM.

USE

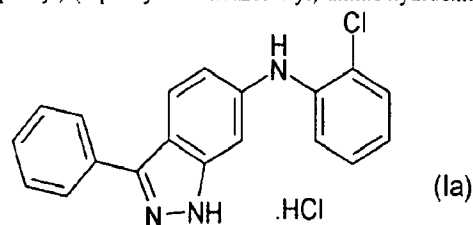
Used central or peripheral neurological degenerative disorders including Alzheimer's disease, cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia Parkinson's type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephalic parkinsonism, progressive supranuclear palsy, Pick's disease, Niemann-Pick's disease, epilepsy, peripheral neuropathy, spinal cord injury, head trauma, cancer, edema, analgesia, fever and pain (e.g. neuromuscular pain, headache, cancer pain, dental pain and arthritis pain) (all claimed).

ADVANTAGE

(I) Are potent inhibitors of JNK, which inhibit the expression of inducible proinflammatory proteins.

SPECIFIC COMPOUNDS

64 Compounds (I) are specifically claimed e.g.:
 (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (Ia).



ADMINISTRATION

The dosage is 0.01-250 mg/kg/day perorally or 0.001-250 mg/kg/day parenterally.

WO 2003068754-A+

(con't)

EXAMPLE

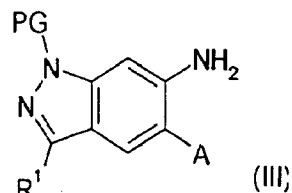
Palladium acetate (15.1 mg) and (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-BINAP) (61.2 mg) were mixed in dry tetrahydrofuran (3 ml) for 5 minutes under a nitrogen atmosphere. 1-Bromo-2-chlorobenzene (75 μ l) and 6-amino-3-phenyl-indazole-1-carboxylic acid tert-butyl ester (199.8 mg) were added, followed by cesium carbonate (295.5 mg). The reaction was stirred at 60°C for 7 hours under a nitrogen atmosphere. Then, additional palladium acetate (15 mg), ((S)-BINAP) (61.4 mg) and 1-bromo-2-chlorobenzene (75 μ l) were added. The reaction mixture was stirred at 60°C for 18 hours, followed by work-up to give 6-(2-chloro-phenylamino)-3-phenyl-indazole-1-carboxylic acid tert-butyl ester.

To a solution of this compound (144.3 mg) in methanol (2 ml) was added 4M HCl in diethylether (1 ml). The reaction mixture was stirred at ambient temperature for 24 hours. The solvent was evaporated and work up produced (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (Ia) (117.1 mg; 87%).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (claimed): Preparation of (I) comprises e.g. reacting an amine compound of formula (III) with R⁵-X

and deprotecting (II: R² = NR⁵R⁶; R⁶ = H) to give (I: R² = NR⁵R⁶; R⁶ = H).



(35pp8032DwgNo.0/0)

WO 2003068754-A/3

2003-679528/64 B02 GLAX 2002.02.05
GLAXO GROUP LTD *WO 2003066632-A1
2002.02.05 2002-002679(+2002GB-002679) (2003.08.14) C07D
471/04, A61K 31/40, A61P 25/00

Use of new and known sulfonyl bicyclic heterocyclic compounds for treating e.g. depression, anxiety, Alzheimer's disease, age related cognitive decline and obesity (Eng)

C2003-185665 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ OM PH PL PT RO RU SC
SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ
VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE
DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR
TZ UG ZM ZW)

Addnl. Data: AHMED M. BROMIDGE S
2003.02.04 2003WO-EP01117

NOVELTY

Sulfonyl bicyclic heterocyclic compounds (I) are used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease,

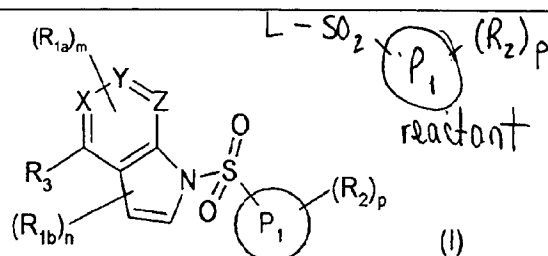
B(6-D1, 6-D5, 6-D8, 14-C1, 14-E11, 14-E12, 14-J1A,
14-J1B, 14-M1, 14-N16) .8

age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia.

DETAILED DESCRIPTION

Sulfonyl bicyclic heterocyclic compounds of formula (I), their salts or solvates, are used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease, age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia.

WO 2003066632-A+



P₁ = aryl or heteroaryl;

R_{1a}, R_{1b} = halo, 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, CN, CF₃, OCF₃, phenyloxy, benzyloxy or 3-6C cycloalkyloxy;

R₂ = aryl or heteroaryl (both optionally substituted by R_{1a} and R_{1b}), halo, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkylthio, 1-6C alkylsulfinyl, 1-6C alkylsulfonyl, 1-6C alkanoyl, CN, CF₃, OCH₂CF₃, OCF₃, OH, 1-6C hydroxyalkyl, 1-6C hydroxyalkoxy, 1-6C alkoxy, 1-6C alkoxy, NO₂, amino, N(1-6C alkyl)₂, NH-1-6C alkyl, 1-6C alkylamino, di-1-6C alkylamino, C(O)OR₄, CONR₅R₆ or NR₅COR₆;

R₄-R₆ = H or 1-6C alkyl, or

R₅ + R₆ = 5-7 membered azacyclic ring optionally containing an

additional N, O or S heteroatom;

R₃ = 5-7 membered heterocyclyl or bicyclic heterocyclyl containing 1-3 N, S or O heteroatoms (both optionally C and/or N-substituted by at least one 1-6C alkyl);

m, n = 0-4;

p = 0-5; and

X, Y, Z = N or C,

provided that one or two of X, Y and Z is N.

INDEPENDENT CLAIMS are also included for:

(1) new compounds (I), excluding 5-bromo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidine and 5-iodo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidine), and

(2) preparation of (I).

ACTIVITY

Antidepressant; Tranquilizer; Nootropic; Neuroprotective; Anorectic; Neuroleptic; Anticonvulsant; Antimigraine; Antiparkinsonian; CNS-Gen.; Anabolic; Eating-Disorders-Gen.; Cerebroprotective; Antiaddictive; Antialcoholic; Antismoking.

WO 2003066632-A+

2003-679528/64

MECHANISM OF ACTION

5-Hydroxytryptamine₆ (5-HT₆) receptor antagonist.

In a test as described in WO98/27081, results showed that 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine hydrochloride (Ia) exhibited good affinity for the 5-HT₆ receptor, having a pK_i value of greater than 8 at human cloned 5-HT₆ receptors.

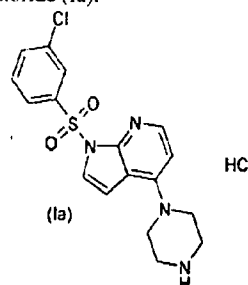
USE

Used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease, age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia (all claimed). (I) Are also used for the treatment of epilepsy, obsessive compulsive disorder, migraine, cognitive memory impairment, Parkinson's disease, sleep disorder (e.g. disturbance of circadian rhythm), feeding disorder (e.g. anorexia and bulimia), panic attack, disorders associated with spinal trauma and/or head injury such as hydrocephalus, and withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines.

SPECIFIC COMPOUNDS

One compound (I) is specifically claimed i.e:

4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperazine hydrochloride (Ia).



ADMINISTRATION

The dosage is 0.05-1000 (especially 20-40) mg orally, parenterally or rectally.

WO 2003066632-A+

(con't)

(C) 2004 Copyright Derwent Information Ltd.

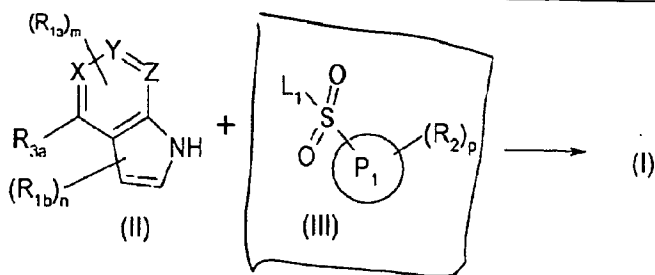
EXAMPLE

t-BuOK (0.15 ml, 1.0 M in tetrahydrofuran (THF)) was added dropwise to an ice cooled solution of 4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-piperazine-1-carboxylic acid tert butyl ester (40 mg) in THF (3 ml) and stirred for 20 minutes. A solution of 3-chlorobenzenesulfonyl chloride (33 mg) in THF (2 ml) was added dropwise and the mixture was warmed to room temperature. Water was added after 3 hours and the mixture extracted by column chromatography to give 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine-1-carboxylic acid tert butyl ester (30 mg).

This compound (25 mg) was exposed to 20% trifluoroacetic acid in dichloromethane for 1 hour. Evaporation *in vacuo*, treatment with 1M hydrochloric acid in diethylether in the presence of methanol and evaporation *in vacuo* produced 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperazine hydrochloride (Ia) (19 mg).

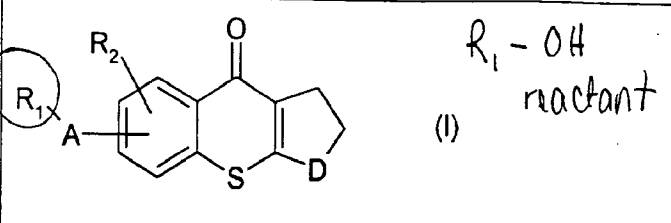
TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of (I) comprises e.g. reacting a bicyclic heterocyclic compound of formula (II) with a sulfonyl compound of formula (III) and optionally deprotecting.

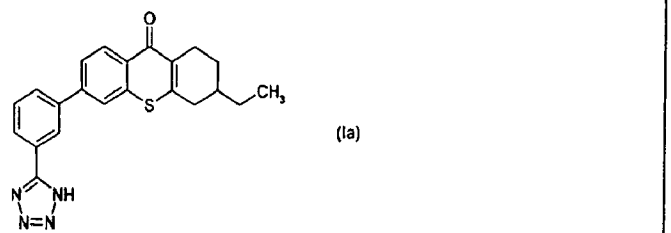


R_{3a} = optionally protected R₃, and
L₁ = a leaving group, preferably halo.
(8pp8021DwgNo.0/0)

WO 2003066632-A/3

<p>2003-211999/21 B02 FARB 2001.05.31 BAYER AG *DE 10126434-A1 2001.05.31 2001-1026434(+2001DE-1026434) (2002.12.05) C07D 335/16, A61K 31/382, C07D 409/04, 409/12, 413/04, 417/12 New tricyclic thiochromenone derivatives as metabotropic glutamate receptor-1 (mGluR1) antagonists useful for treating e.g. hemorrhagic stroke and atherosclerosis, especially pain or neurodegenerative diseases C2003-054276 Addnl. Data: MEIER H, ALLERHEILIGEN S, GERISCH M, SCHOE- LOOP R, VOERSTE A, MAULER F, DE VRY J, MUELLER T, METHFESSEL C</p>	<p>B(6-B2, 14-A1, 14-A2, 14-C1, 14-E5, 14-E12, 14-F2D1, 14-F4, 14-F7, 14-F8, 14-F10, 14-G2D, 14-H1, 14-J1A, 14-J1B, 14-J5, 14-J7, 14-L6, 14-M1, 14-N1, 14-N16, 14-S1, 14-S4) .12</p>  <p>(I)</p> <p>$R_1 = \text{OH}$ reactant</p>
<p><u>4NOVELTY</u> Tricyclic thiochromenone derivatives (I) are new.</p> <p><u>DETAILED DESCRIPTION</u> Thiochromenones of formula (I) and their salts, hydrates and/or solvates are new;</p>	<p>$R_1 =$ (i) 6-10C aryl or 5-10 membered heteroaryl (both optionally substituted (os) by one or more of halo, CHO, CONH₂, CN, OH, OCF₃, NO₂, NR₃R₄, tetrazolyl or alkoxycarbonyl; or alkyl, alkoxy, 1-6C acyl or alkylthio (all os by OH, morpholinyl, 1-6C acyloxy or halo)); (ii) 3-12 membered carbocyclyl or 4-2 membered heterocyclyl (both os by one or more of alkyl, alkoxy, 1-6C acyl, alkoxycarbonyl or oxo); or (iii) R₅-E; A = direct bond, O, S, NR₆, CO, SO, SO₂, SO₂O, CONR₇, SO₂NR₈, OSO₂, NR₉CO, NR₁₀SO₂, R₁₁SO₂O, NR₁₂SO₂NR₁₃ or</p> <p style="text-align: right;"> DE 10126434-A+</p>

<p>NR₁₅CONR₁₅; or R₁A- = H or NH₂; R₃, R₄ = H, alkyl or 1-6C acyl; E = optionally unsaturated 1-10C alkanediyl; R₅ = H, CONH₂, halo, OH, NO₂, CF₃, NH₂, mono- or dialkylamino, alkoxy, 6-10C aryl, 5-10 membered heteroaryl or 4-10 membered heterocyclyl (os by oxo and/or alkyl and optionally benzo-fused), where aryl, heteroaryl and benzo groups are os by halo, CN, CF₃, OCF₃, NO₂ or alkyl; R₆ - R₁₅ = 3-8C cycloalkyl or optionally unsaturated alkyl (os by OH, phenyl (os by halo or 1-4C alkyl), alkoxy, alkoxycarbonyl or cycloalkyl); R₆, R₇, R₉ - R₁₂, R₁₄, R₁₅ = H; R₂ = H, halo, or alkyl or alkoxy (both os by 1 or 2 of OH, alkoxy or mono- or dialkylamino); D = 3-10C hydrocarbylene (os by F). Alkyl moieties have 1-6C unless specified otherwise. Provided that: (1) the -R₁A- group is in the 2- or 3-position of the thiochromenone ring; and (2) the compound 2-chloro-6,7,8,9,10,10a-hexahydro-cyclohepta(b)thiochromen-11(5aH)-one is excluded:</p>	<p><u>ACTIVITY</u> Neuroprotective; Cerebroprotective; Immunosuppressive; Anticonvulsant; Antiarteriosclerotic; Antidepressant; Nootropic; Antiparkinsonian; Virucide; Antibacterial; Tranquilizer; Neuroleptic; Antidiabetic; Antiemetic; Anorectic; Antiaddictive; Analgesic.</p> <p><u>MECHANISM OF ACTION</u> Metabotropic Glutamate Receptor-1 (mGluR1 receptor) Antagonist. In receptor binding assays using CHO cells expressing the mGluR1 receptor, 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia) had an IC₅₀ of 9 nM.</p> <p><u>USE</u> (I) are used as medicaments (claimed), useful for the treatment and/or prophylaxis of neuronal damage diseases or diseases associated with disorders of the glutamatergic system in the central and peripheral nervous system, specifically: (i) neuronal damage associated with ischemic, thrombotic, thrombo-embolic or hemorrhagic stroke, direct or indirect cerebral-cranial injury or post-operative cerebral ischemia; (ii) primary or secondary cerebral</p> <p style="text-align: right;"> DE 10126434-A+1</p>
--	--

<p>2003-211999/21</p> <p>disorders, e.g. associated with cerebral vasospasm, hypoxia/anoxia, preinatal asphyxia, autoimmune, metabolic or organ diseases, convulsions, atherosclerosis or arteriosclerosis; (iii) chronic or psychiatric disorders such as depression, neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease or Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, neurodegeneration due to viral or bacterial infections or multi-infarct dementia; (iv) dementia of various origins, cerebral insufficiency in the elderly, memory disorders, bone marrow injury, anxiety states, drug-induced Parkinsonian syndrome, psychosis (e.g. schizophrenia), cerebral edema, neuronal damage after hypoglycemia, emesis, nausea, obesity, substance abuse and withdrawal symptoms, CNS-mediated spasms, sedation or movement disorders; or (v) acute and/or chronic pain, especially cancer-induced pain or chronic neuropathic pain. (I) are especially used for the treatment and/or prophylaxis of pain or neurodegenerative diseases (claimed).</p> <p><u>SPECIFIC COMPOUNDS</u> 165 Compounds (I) are disclosed, e.g. 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia).</p>	 <p>(Ia)</p> <p><u>ADMINISTRATION</u> Dosage is 0.001-10 mg/kg, preferably 0.005-3 mg/kg in the case of oral administration. (I) are preferably administered orally, parenterally or transdermally, although inhalative or topical administration is also possible.</p> <p><u>EXAMPLE</u> A mixture of 0.5 g 3-ethyl-9-oxo-2,3,4,9-tetrahydro-1H-thioxanthen-6-carbonitrile, 0.51 g triethylammonium hydrochloride</p> <p style="text-align: right;"> DE 10126434-A+2</p>
---	---

(con't)

and 0.24 g sodium azide was stirred in toluene overnight at 100 °C, cooled, stirred with water and toluene, acidified to pH 3 with hydrochloric acid and further stirred. The obtained solid was filtered off, washed with water, dried and recrystallized from cyclohexane/ethyl acetate to give 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-xanthen-9-one (Ia; 290 mg; 50%).

DEFINITIONS

Preferred Definitions:

R_1 = (i) phenyl or 5- or 6-membered heteroaryl (both os by 1 or 2 of halo, CN or 1-3C alkyl); or (ii) 5-7 membered heterocyclyl (os by one or more of 1-3C alkyl or oxo);

A = direct bond, NR_6 , SO_2NR_8 or NR_9CO ;

R_6 , R_8 , R_9 = optionally unsaturated 1-3C alkyl (os by 1 or 2 of OH or OMe) or H;

R_2 = H;

D = $(CH_2)_m-CR_{16}R_{17}-(CH_2)_n$ (having a total of 3-6C);

m, n = 0-2;

R_{16} , R_{17} = H or 1-3C alkyl;

$CR_{16}R_{17}$ = 3-6C cycloalkylidene;

The - R_1A - group is in the 3-position.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are generally prepared by introducing and/or modifying the group - AR_1 . Typically a corresponding halo compound having - AR_1 replaced by Br or Cl is reacted with:

- (i) a boron compound of formula $R_{19}-BR_{20}R_{21}$ (III) in a solvent in presence of a catalyst (preferably under Suzuki coupling conditions) to give (I; - $AR_1 = R_{19}$);
- (ii) a heterocyclic compound of formula $R_{22}-H$ (IV) in a solvent to give (I; - $AR_1 = R_{22}$); or
- (iii) an active hydrogen compound of formula R_1-G-H (V) in a solvent in presence of a catalyst to give (I; A = G).

R_{19} = as for R_1 (i);

R_{20} , R_{21} = OH;

$BR_{20}R_{21}$ = 3,3,4,4-tetramethyl-1-bora-2,5-dioxacyclopentane;

R_{22} = N-bonded 4-12 membered heterocyclyl (os as in R_1 (ii));

G = O, S or NR_6 .

(88pp2400DwgNo.0/0)

DE 10126434-A/3

2002-732620/79 B02 SMIK 2000.11.24
SMITHKLINE BEECHAM PLC *WO 200241889-A2
2001.06.04 2001-013517(+2000GB-028708) (2002.05.30) A61K
31/404, A61P 25/24

Composition useful for the treatment of e.g. depression comprises new and known indole compounds and a carrier (Eng)

C2002-207206 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG
SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA
ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH
GM GR IE IT KE LS LU MC MW MZ NL OA PT SD
SE SL SZ TR TZ UG ZM ZW)

Addnl. Data: BROMIDGE S M
2001.11.16 2001WO-EP13411, 2001.06.04 2001GB-013517

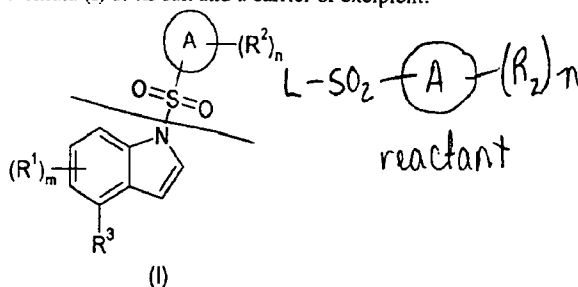
NOVELTY

A composition comprises a new or known indole compound (I) and a carrier or excipient.

B(6-D1, 14-E10, 14-E10C, 14-E11, 14-J1A1, 14-J1A4,
14-J1B, 14-J1B3, 14-J1B4, 14-J7, 14-L6, 14-M1A, 14-M1B, 14-M1C)
.5

DETAILED DESCRIPTION

A composition comprises a new or known indole compound of formula (I) or its salt and a carrier or excipient.



Ring A = phenyl, naphthyl or heteroaryl;

R¹ = Q, phenyloxy, benzyloxy or 3-6C cycloalkyloxy;

Q = halo, 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, CN, CF₃ or OCF₃;

R² = Q, 3-6C cycloalkyl, 1-6C alkylthio, 1-6C alkylsulfinyl, 1-6C

WO 200241889-A+

alkylsulfonyl, OCH₂CF₃, OH, hydroxy-1-6C alkyl, hydroxy-1-6C alkoxy, 1-6C alkoxy, 1-6C alkoxy, 1-6C alkoxy, 1-6C alkoxy, nitro, amino, N-(1-6C alkyl)₂, NH-1-6C alkyl, 1-6C alkylamino, di-1-6C alkylamino, C(O)OR⁴, CONR⁵R⁶, NR⁵COR⁶, or phenyl, naphthyl or heteroaryl (all optionally substituted by R¹);

R⁴, R⁶ = H or 1-6C alkyl; or

R⁵, R⁶ = 5-7 membered azacyclic ring optionally containing an additional N, S or O;

R³ = 5-7 membered mono- or bicyclic heterocyclic ring containing 1-3 N, S and/or O and optionally substituted by at least one 1-6C alkyl;

m = 0-4; and

n = 0-5.

INDEPENDENT CLAIMS are also included for:

- (1) New compounds (I) and their salts, excluding 4-(1-methyl-4-piperidinyl)-1-(phenylsulfonyl)-1H-indole, 4-(1,3-dithian-2-yl)-1-[4-methylphenylsulfonyl]-1H-indole, or 1-[(4-methylphenylsulfonyl)-4-(4-morpholinyl)-1H-indole; and
- (2) preparation of new compounds (I).

ACTIVITY

Antidepressant; Tranquilizer; Nootropic; Neuroprotective;

Neuroleptic; Anticonvulsant; Antimigraine; Antiparkinsonian; Antiaddictive; Anorectic; Antiinflammatory.

MECHANISM OF ACTION

5-HT₆ receptor antagonist.

USE

In therapy or in the manufacture of medicament for the treatment of depression, anxiety, cognitive memory disorders, Alzheimer's disease, age-related cognitive decline, mild cognitive impairment, attention deficit disorder/hyperactivity syndrome, and schizophrenia (all claimed). Also useful for the treatment of epilepsy, obsessive compulsive disorders such as anorexia and bulimia, panic attack, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepine disorders associated with spinal trauma and/or injury such as hydrocephalus; and in the treatment of certain gastrointestinal disorder such as irritable bowel syndrome.

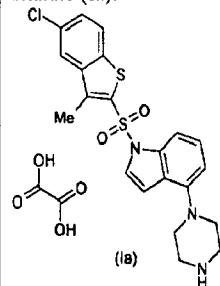
SPECIFIC COMPOUNDS

175 Compounds (I) are specifically claimed, e.g. 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole

WO 200241889-A+/1

2002-732620/79

oxalate (Ia).



ADMINISTRATION

Administration of (I) is 0.05-1000 (preferably 0.2-5) mg, more than once (preferably 2-3) times a day orally, parenterally or rectally.

EXAMPLE

To a solution of 4-(4-benzyl-piperazin-1-yl)-1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-1H-indole (93 mg) in dry 1,2-

dichloromethane (5 ml) was added N,N-diisopropylethylamine (0.16 ml) and 1-chloroethyl chloroformate (0.09 ml). The solution was stirred at 80 °C under argon for 50 minutes and then concentrated *in vacuo*. The residue was redissolved in methanol (10 ml) and the solution was refluxed for 1.3 hours. After concentrating the mixture, the residue was redissolved in dichloromethane (15 ml) and the solution was washed. The organic phase was dried, concentrated and chromatographed to give a free base (55 mg) of 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole (Ia'). Treatment of a solution of (A) in DCM (1 ml) with an oxalic acid solution (1.5 equivalents) in methanol/diethyl ether gave 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole oxalate (Ia).

DEFINITIONS

Preferred Definitions:

R¹ = unsubstituted piperazine ring;

R¹ = 5,7-dichloro;

Ring A = phenyl;

WO 200241889-A+/2

(con't)

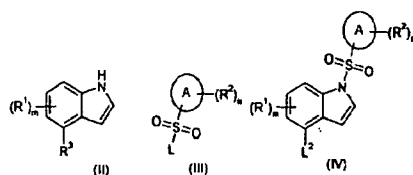
(C) 2004 Copyright Derwent Information Ltd.

$n = 1$; and
 $R^2 = Cl$.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of new compounds (I) comprises:

- (1) coupling a compound of formula (II) or its protected derivative with a compound of formula (III) or its protected derivative; removing any protecting groups; and forming a salt;
- (2) preparing (I; R^3 = optionally substituted piperazinyl or 1,4-diazepanyl group linked to the indole moiety *via* N) by reacting a compound of formula (IV) or its protected derivative with a compound of formula R^3-H and optionally removing any protecting group and forming a salt;
- (3) deprotecting protected compounds (I); or
- (4) interconversion of (II) to its salt or derivatives.



L = leaving group;

L^2 = leaving group (preferably halo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy); and

R^3 = optionally protected and/or substituted piperazinyl or 1,4-diazepanyl group.

(44pp8019DwgNo.0/0)

WO 200241889-A/3

2002-691750/74 B03 (B02) FARB 2001.03.05

BAYER AG *WO 200270484-A1

2001.03.05 2001-1010438(+2001DE-1010438) (2002.09.12) C07D

213/85, A61K 31/4418, 31/443, C07D 405/04, 417/12, 409/12, A61K

31/4436, A61P 9/00

Adenosine receptor-specific ligand medicaments, comprising new or known 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarbonitrile derivatives, useful e.g. for treating cardiovascular diseases, cancer, inflammation, pain or diabetes (Ger)

C2002-195540 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US VZ VN YU ZA ZM ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW)

Addnl. Data: ROSENTER U, KRAEMER T, VAUPEL A,

HUEBSCH W, DIEDRICHS N, KRAHN T,

DEMBOWSKY K, STASCH J

2002.02.20 2002WO-EP01758

B(6-H, 7-D4B, 14-C1, 14-C3, 14-D2, 14-F1, 14-F2, 14-F4, 14-F7, 14-H1, 14-J1A3, 14-J1A4, 14-K1, 14-N7, 14-N12, 14-N16, 14-N17, 14-P2, 14-S4) .11

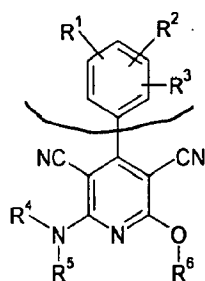
NOVELTY

The use of 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarbonitrile derivatives (I) for the prophylaxis and/or treatment of diseases is new. Compounds (I) are new, with some specific exclusions.

DETAILED DESCRIPTION

Pyridine derivatives of formula (I) and their salts, hydrates, hydrated salts and solvates are claimed for the prophylaxis and/or treatment of diseases.

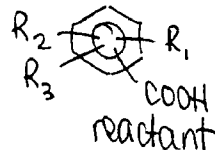
WO 200270484-A+



(I)

R₁ - R₃ = alkyl (optionally substituted (os) by 1-3 of OH, OT, cycloalkyl, alkenyl, alkynyl, halo or aryloxy); aryl (os by 1-3 of halo, NO₂, OT, COOH, COOT, NHT or NT₂); alkoxy (os by 1-3 of OH, OT, 3-6C cycloalkyl, alkenyl, alkynyl, aryl, Het, aryloxy, halo, CN, COOT, NH₂, NHT or NT₂); or H, OH, halo, NO₂, CN or -NHCOR₇;

or R₁ + R₂ (on adjacent C) = group completing a 5-7 membered saturated or partially unsaturated heterocycle containing 1 or 2 of N, O and/or S as heteroatom(s) (os by T or =O);



T = 1-4C alkyl;

Het = 5-10 membered heteroaryl containing 1-3 of N, O and/or S as heteroatom(s);

R₇ = alkyl (os by OH or OT), cycloalkyl or aryl (os as in R₁);

R₄, R₅ = H, alkyl (os by OH, OT, cycloalkyl, aryl or Het') or 3-8C cycloalkyl (os by OH or alkyl);

or NR₄R₅ = 5-7 membered saturated or partially unsaturated heterocycle (optionally containing 1 or 2 of N, O and/or S as further heteroatom(s) and os by 1-3 of =O, F, Cl, OH, 1-6C alkyl or 1-6C alkoxy);

Het' = 5- or 6-membered heteroaryl containing 1-3 of N, O and/or S as heteroatom(s);

R₆ = cycloalkyl or alkyl (os by cycloalkyl, OH, OT, alkenyl, alkynyl, aryl or Het, aryl and Het themselves being os by halo, T, OT, NH₂, NHT, NT₂, NO₂, CN or OH);

unless specified otherwise alkyl moieties have 1-8C, alkenyl or alkynyl moieties 2-4C, cycloalkyl moieties 3-7C and aryl moieties 6-10C.

INDEPENDENT CLAIMS are included for:

(i) (I) (including salts etc.) as new compounds, with the exception of (I; R₁ - R₅ = H; R₆ = Me, Et, propyl or isopropyl), (I; R₁ = 4-Me, 4-OMe, 2-Cl, 4-Cl, 3-Me or 2-OH; R₂ - R₅ = H; R₆ = Et), (I; R₁ = 4-F

WO 200270484-A+I

2002-691750/74

or 4-OMe; R₂ - R₅ = H; R₆ = Me) or (I; R₁ + R₂ = OCH₂O; R₃ - R₅ = H; R₆ = Me); and

(ii) the preparation of the new compounds (I).

ACTIVITY

Cardiant; vasotropic; hypotensive; antiarteriosclerotic; antianginal; thrombolytic; anticoagulant; cerebroprotective; uropathic; cytostatic; antiinflammatory; antiasthmatic; dermatological; neuroprotective; nootropic; antiparkinsonian; analgesic; hepatotropic; antidiabetic; vulnerary.

MECHANISM OF ACTION

Adenosine receptor-specific ligand. (I) are in general selective ligands for adenosine-A₁, -A_{2a} and/or -A_{2b} receptors; in particular (I; R₁ + R₂ = OCH₂O, OCH₂CH₂O or O(CH₂)₃O) are selective for A₁ receptors and (I; one of R₁ - R₃ = NHCOR₇; one of R₄ and R₅ = benzyl or pyridylmethyl) are selective for A₁ and/or A_{2b} receptors. The ligands may be agonists or antagonists.

USE

(I) are especially used for the treatment and/or prophylaxis of cardiovascular diseases, urogenital diseases, cancer, inflammatory or neuroinflammatory diseases, pain, respiratory tract diseases, liver fibrosis, liver cirrhosis or diabetes (all claimed). Specific disorders to be controlled include coronary heart disease, hypertension, restenosis, arteriosclerosis, tachycardia, arrhythmia, stable or unstable angina pectoris, atrial flutter, thromboembolic disease, myocardial infarction, cerebral stroke, transitory ischemic attacks, bladder irritation, erectile dysfunction, female sexual dysfunction, asthma, inflammatory dermatosis, Alzheimer's disease, Parkinson's disease, chronic bronchitis, pulmonary emphysema, bronchiectasis, cystic fibrosis, pulmonary hypertension, diabetes mellitus or wound healing deficiency.

ADVANTAGE

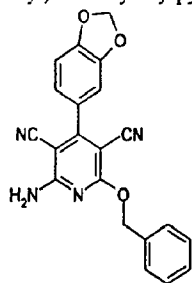
(I) have higher selectivity for particular adenosine receptor subtypes than prior art compounds

SPECIFIC COMPOUNDS

WO 200270484-A+2

(con⁴)

20 Compounds (I) are disclosed, e.g. 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzyloxy-pyridine-3,5-dicarbonitrile (Ia).



(Ia)

ADMINISTRATION

Dosage is 0.1-10000 (preferably 1-100) $\mu\text{g/kg}$ parenterally or 0.1-10 (preferably 1-4) mg/kg orally. (I) may also be administered locally.

EXAMPLE

A solution of 344 mg sodium in 20.7 ml benzyl alcohol was treated with 660 mg malonodinitrile and 750 mg piperonal, stirred for 16 hours at room temperature, neutralized and partitioned between

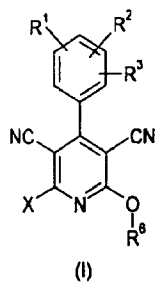
water and dichloromethane. The organic phase was worked up to give, after chromatographic purification, 872 mg (40.1%) of 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzyloxy-pyridine-3,5-dicarbonitrile (Ia).

TECHNOLOGY FOCUS

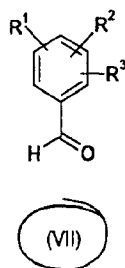
Organic Chemistry - Preparation: Three methods of preparation of (I) are claimed. Typically (a) a pyridine derivative of formula (II) is reacted with an amine of formula NHR_4R_5 (III); or (b) a benzaldehyde derivative of formula (VII) is reacted with malonodinitrile and an alcohol of formula R_6OH (VI) in presence of a base to give (I; $\text{R}_4, \text{R}_5 = \text{H}$).

WO 200270484-A+3

2002-691750/74



(I)



(VII)

X = leaving group.
(80pp2400DwgNo.0/0)

WO 200270484-A/4

2002-599296/64 B02 MERI 2000.10.12
MERCK & CO INC *WO 200236734-A2

2000.10.12 2000-239732P(+2000US-239732P) (2002.05.10) C12N
New aza- and polyaza-naphthalenyl ketones useful in the
treatment of e.g. infection by HIV (Eng)

C2002-169132 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA
ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH
GM GR IE IT KE LS LU MC MW MZ NL OA PT SD
SE SL SZ TR TZ UG ZW)

Addnl. Data: ZHUANG L, WAI J S, PAYNE L S, YOUNG S D,
FISHER T E, EMBREY M, GUARE J P
2001.10.09 2001 WO-US42553

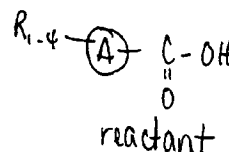
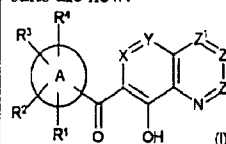
NOVELTY

Aza- and polyaza-naphthalenyl ketones or their salts are new.

DETAILED DESCRIPTION

B(6-H, 11-C1C, 11-C7, 12-K4, 14-A2B1, 14-G1B, 14-L6) .7

Aza- and polyaza-naphthalenyl ketones of formula (I) or their salts are new.



A = phenyl optionally fused to a carbocycle to form a fused carbocyclic ring, or a heterocycle containing at least one heteroatom selected from N, O, or S and balance of carbon atoms, with at least one of the ring atom being carbon (all optionally substituted by R¹ - R⁴);

X = N or C-Q¹;

Y = N or C-Q²;

Z¹ = N or C-Q³;

Z² = N or C-Q⁴;

Z³ = N or CH;

Q¹ - Q⁴ = T, T', H, 2-5C alkynyl, 2-5C alkynyl-CH₂N(R_a)₂, 2-5C

|WO 200236734-A+

alkynyl-CH₂N(OR_a), -N(R_a)-C(NR_a)-N(R_a)₂ or 1-6C
(fluoro)alkyl substituted with R_k, -O-(1-4C)alkyl-R_k, -N(R_c)-
R_k, -N(R_c)(1-6C)alkyl substituted with 1 or 2 R_k, -N(R_c)(1-
6C)alkyl-OR_k, -C(=O)N(1-6C)alkyl-R_k, or (2-5C)alkynyl-
CH₂S(O)_n-R_a;

T = 1-6C alkyl, 1-6C fluoroalkyl, OH, -O(1-6C)alkyl, O-(1-
6C)fluoroalkyl, halo, CN;

T' = 1-6C alkyl-O(R_a), 0-6C alkyl-C(=O)R_a, 0-6C alkyl-CO₂R_a, 0-6C
alkyl-S(R_a), -N(R_a)₂, 1-6C alkyl-N(R_a)₂, 0-6C alkyl-
C(=O)N(R_a)₂, 1-6C alkyl-N(R_a)C(R_a)=O, -SO₂R_a, -N(R_a)SO₂R_a, -
N(R_a)-(1-6C)alkyl-N(R_a)₂, -N(R_a)(1-6C)alkyl-N(R_a)-C(R_a)=O, -
R_k, -N(R_a)(1-6C)alkyl-SR_a, -N(R_a)(1-6C)alkyl-OR_a, 2-5C
alkenyl-R_k, 2-5C alkynyl-R_k, -O-R_k, -O-(1-4C)alkyl R_k, -S(O)_n-
R_k, -S(O)_n(1-4C)alkyl-R_k, -O(1-6C)alkyl-OR_k, -O(1-6C)alkyl-
O(1-4C)alkyl-R_k, -O(1-6C)alkyl-SR_k;

R¹ and R² = T, T', H, -NO₂, (2-5C)alkenyl, Q(1-6C)-OR_a, -O(1-
6C)alkyl-SR_a, O(1-6C)alkyl-NH-CO₂-(R_a), -O(2-
6C)alkyl-N(R_a)₂ or 1-6C (fluoro)alkyl mono- or di-
substituted with 1 or 2 R_k, -O-(1-4C)alkyl-R_k, -O-(1-
6C)alkyl(OR_b)R_k, 1-6C alkyl (OR_b)(1-4C alkyl-R_k), 0-
6C alkyl-N(R_b)(1-4C alkyl-R_k), 0-6C alkyl S(O)_n-R_k, 1-
6C alkyl-S(O)_n(1-4C)alkyl-R_k, (0-6C)alkyl-C(O)-R_k or O-

6C alkyl-C(O)-(1-4C)alkyl-R_k;

R₃ and R₄ = T, H, -NO₂, (1-6C)alkyl-OR_a, (0-6)alkyl-C(=O)R_a, (0-
6C)alkyl-CO-2R_a, (0-6C)alkyl-SR_a, -N(R_a)₂, 1-6C alkyl-
N(R_a)₂, 0-6C alkyl-C(=O)N(R_a)₂, -SO₂(R_a), -
N(R_a)SO₂(R_a), 2-5C alkenyl, O(1-6C)alkyl-OR_a, O(1-
6C)alkyl-S(R_a), O(1-6C)alkyl-NH-CO₂R_a, O(2-6C)alkyl-
N(R_a)₂ or oxo;

R_a = H or 1-6C (fluoro)alkyl;

R_b = H, 1-4C (fluoro)alkyl, -R_k, 2-3C alkenyl, 1-4C alkyl-R_k, 2-3C
alkenyl-R_k, -S(O)_n-R_k, or -C(O)-R_k;

R_c = H, 1-6C alkyl, 1-6C alkyl substituted with -N(R_a)₂, or 1-4C alkyl-
aryl (aryl is optionally mono- to penta-substituted by T, or -S(1-
6C)alkyl);

R_k = carbocycle or heterocycle (optionally mono- to penta-substituted
by T, -S-(1-6C)alkyl, oxo, -(CH₂)₀₋₃-C(=O)N(R_a)₂, -(CH₂)₀₋₃-
C(=O)-R_a, -N(R_a)-C(=O)OR_a, -N(R_a)-C(=O)OR_a, -
(CH₂)₁₋₃N(R_a)-C(=O)-R_a, aryl, aryloxy, (1-4C)alkyl substituted
with aryl, heteromonocycle, (1-4C)alkyl substituted with a
heteromonocycle, heteromonocyclylcarbonyl-(0-6C)alkyl, N-
heteromonocyclyl-N(1-6C)alkyl-amino-(where aryl, aryloxy,
(1-4C)alkyl substituted by aryl (optionally substituted by halo,

|WO 200236734-A+1

2002-599296/64

(1-6C)alkyl, -O-(1-6C)alkyl, (1-6C)alkyl substituted by N(R_a)₂,
1-6C fluoroalkyl or -OH) and heteromonocycle, (1-4C)alkyl
substituted by a heteromonocycle, heteromonocyclyl-carbonyl(0-
6C)alkyl, N-heteromonocyclyl-N(1-6C)alkyl-amino(optionally
substituted by mono- to tri-halo, 1-6C alkyl, -O-(1-6C)alkyl, 1-
6C fluoroalkyl, oxo or OH));

n = 0 - 2.

Provided that:

(1) X and Y are not both N;

(2) when A is phenyl, or X, Y and Z¹ - Z³ is CH, then at least one of R¹ - R⁴ is not H;

(3) when A is phenyl, X is CH, Y is CQ² (where Q² is halo, 1-6C alkyl or phenyl optionally substituted by halo, 1-6C alkyl or benzyl (optionally substituted by halo, or 1-6C alkyl)), Z¹ - Z³ is CH, and one of R¹ - R⁴ is H, halo, or 1-6C alkyl, then the other of R¹ - R⁴ is not H, halo, or 1-6C alkyl;

(4) when A is phenyl, or X, Y and Z¹ - Z³ is CH, then at least one of R¹ - R⁴ is not H; and

(5) when A is phenyl, X is CH, Y is CH, Z¹ is CQ³, Z² and Z³ is CH, then either Q³ is not substituted by benzyl or at least one of R¹ - R⁴

is not H.

ACTIVITY

Anti-HIV; Virucide.

MECHANISM OF ACTION

HIV integrase and HIV replication inhibitors.

USE

In the treatment or prevention of infection by HIV; treating, preventing or delaying onset of AIDS (claimed) or AIDS related complications (ARC). The compounds are also useful in the preparation and execution of screening assay for antiviral compounds; for isolating enzyme mutants; and in establishing or determining the binding site of other antiviral to HIV integrase e.g. by competitive inhibition.

ADVANTAGE

The compounds have highly specific inhibition capacity of HIV

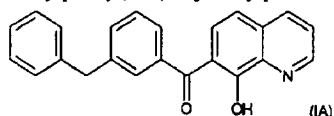
|WO 200236734-A+2

(con't)

integrase and HIV replication.

SPECIFIC COMPOUNDS

25 compounds are specifically claimed as (I) e.g. 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methanone (IA)



ADMINISTRATION

The compounds are administered orally, parenterally (including subcutaneous injection, intravenous, intramuscular, intrasternal injection, or infusion). Dosage is from 0.1 - 1000 (especially 0.5 - 100) mg/kg body weight in divided form.

EXAMPLE

A septum was added to tert-butylamine (7.24 ml) in toluene (50 ml). The reaction was cooled to 78°C and bromine (1.69 ml) was added, stirred for 10 minutes followed by addition of 8-

hydroxyquinoline (5 g) in chloroform (10 ml). The addition mixture was stirred for 1 hour, warmed to ambient temperature, diluted with ethyl acetate (200 ml) and extracted. The organic extracts were dried, filtered and purified to give 7-bromoquinolin-8-ol (A). (A) (3.1 g), diisopropylethylamine (7.23 ml) and methyl chloride (100 ml) were added. MEM chloride (1.90 ml) was added and the reaction was stirred for 18 hours. After which another MEM chloride (0.95 ml) was added. This mixture was stirred for 1 hour, water (50 ml) was added and the organic solvent removed in vacuum. The residue was extracted, washed dried and filtered to give 7-bromo-8-(2-methoxyethoxymethoxy)-quinoline (B). (B) (0.766 g) and tetrahydrofuran (THF) (10 ml) were added in flask. The flask was cooled to -78°C and to it was added t-butyllithium (3.6 ml of a 1.5M solution in pentane, 5.4 mmol). The reaction was stirred for 15 minutes then N-methyl-N-methoxy-(3-benzyl)benzenecarboxamide (0.626 g) THF (5 ml) was added at 74°C. This mixture was stirred for 5 minutes, warmed to ambient temperature and the reaction was quenched by the addition of saturated aqueous NH₄Cl. The solution was extracted, washed, dried and filtered to give 1-(3-benzylphenyl)-8-[(2-methoxyethoxy)methoxy]quinolin-7-yl)methanone (C). (C) (0.2 g), MeOH (3 ml) and trifluoroacetic acid (1.081 ml) were added and the

WO 200236734-A+/3

2002-599296/64

reaction was stirred for 3 days, after which time it was poured into aqueous saturated NaHCO₃ (20 ml) and extracted, dried, filtered and purified to give 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methanone.

DEFINITIONS

Preferred Definitions:

X = N;
Y = C-Q²;
Z¹ = C-Q³;
Z² = C-Q⁴;
Z³ = CH;
Q³ and Q⁴ = H;
R¹ = -R_k, (CH₂)₁₋₄-R_k, -OR_k, or -O-(CH₂)₁₋₄-R_k;
R² = H, methyl, ethyl, CF₃, methoxy, ethoxy, -OCF₃, F, Cl, Br, -CN, -CH₂OR_k, -CO₂R_k, -SR_k, -N(R_k)₂, -(CH₂)₁₋₃N(R_k)₂, -SO₂R_k, -(CH₂)₁₋₂-N(R_k)-C(R_k)=O, -R_k, -(CH₂)₁₋₄-R_k, -OR_k or -O-(CH₂)₁₋₄-R_k;
R_k = S¹, S², S³ or S⁴;
S¹ = phenyl (optionally mono- to tetra-substituted by T¹, -S-CH₃,

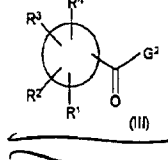
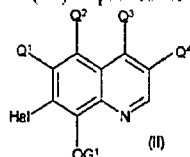
phenyloxy (optionally mono- to tri-substituted by halo, methyl, -CF₃, OH), -N(R_k)₂, -(CH₂)₁₋₃N(R_k)₂, (CH₂)₁₋₃N(R_k)₂, -R_k, -(CH₂)₀₋₃C(=O)N(R_k)₂ or (CH₂)₀₋₃C(=O)R_k;
T¹ = F, Cl, Br, methyl, -CF₃, methoxy, OCF₃, phenyl, OH or CN;
S² = 3-6C cycloalkyl (optionally mono- to tri-substituted by T¹);
S³ = 5 or 6 membered ring selected from thienyl, pyridyl, imidazolyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, furanyl or pyridazinyl (optionally substituted on N or C by mono or di T¹, -S(1-6C)alkyl, phenyloxy (optionally substituted by F, Cl, Br, methyl, -CF₃, or OH), -N(R_k)₂, 1-6C alkyl-N(R_k)₂, -R_k, oxa, -(CH₂)₀₋₃C(=O)N(R_k)₂ or -(CH₂)₀₋₃C(=O)R_k;
S⁴ = 5 - 6 membered T (optionally mono- or di-substituted by T¹, =O, benzyl, phenylethyl, -(CH₂)₀₋₃-C(=O)N(R_k)₂, -(CH₂)₀₋₃C(=O)R_k, N(R_k)-C(=O)R_k, N(R_k)-C(=O)OR_k, N(R_k)-C(=O)OC(CH₃)₃, (CH₂)₁₋₃N(R_k)-C(=O)R_k, N(R_k)₂, (CH₂)₁₋₃N(R_k)₂, (CH₂)₀₋₃C(=O)R_k, -R_k, -N(R_k)₂ or (CH₂)₁₋₃R_k);
T = piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl,

WO 200236734-A+/4

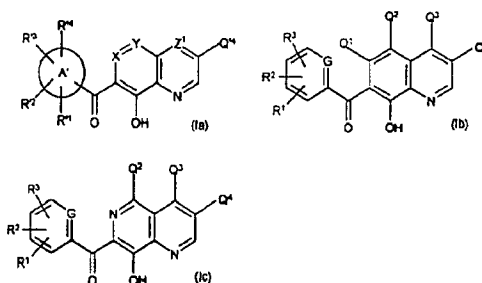
imidazolidinyl, piperazinyl, tetrahydrofuran or pyrazolidinyl
R_i = T (optionally substituted by F, Cl, Br, oxo, methyl or methoxy).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) are prepared by treating (II) with alkylolithium, followed by coupling of (II) with carboxylic derivative of (III) to provide ketone of formula (I).



G¹ = alkyl;
Hal = halogen; and
G² = OH, alkoxy, halide, NMe(OMe).
Preferred Compound: The ketones are of formula (Ia) (preferably (Ib), especially (Ic)).



A' = phenyl, a fused carbocyclic ring selected from indan, 1-H indene, naphthalene, 1,2-dihydro-naphthalene, 1,2,3,4-tetrahydro-naphthalene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 6,7-dihydro-5H-benzocycloheptene, 9H-fluorene, anthracene, or 9,10-Dihydro-anthracene, 5- or 6-membered optionally saturated monocyclic heterocycle containing 1 - 4 N atoms, or 0 - 2 O or S atoms with at least one of the ring atoms being carbon (all optionally substituted by R¹ - R⁴);
Q¹ = H or 1-4C alkyl;
Q² = T₁, T₂, 2-3C alkynyl, -C equivalent to C-CH₂N(R_k)₂, -C

WO 200236734-A+/5

(cont)

equivalent to C-CH₂OR_a, -N(R_c)-R_k, -N(R_c)(1-4C)alkyl substituted with 1 or 2 R_k, -N(R_c)(1-4C)alkyl-OR_k, -C(=O)N(1-4C)alkyl-R_k, -C equivalent to C-CH₂SR_a, or -C equivalent to C-CH₂SO₂R_a;

T₁ = H, 1-4C (fluoro)alkyl, -O-1-4C (fluoro)alkyl or CN;

T₂ = OH, halo, -1-4C alkyl-OR_a, -(CH₂)_{0.2}C(=O)R_a, -(CH₂)_{0.2}CO₂-R_a, -N(R_a)₂, 1-4C alkyl-N(R_a)₂, -(CH₂)_{0.2}C(=O)N(R_a)₂, (1-4C)alkyl-N(R_a)-C(R_a)=O, -SO₂-R_a, -N(R_a)SO₂R_a, -N(R_a)(1-4C)alkyl-SR_a, -N(R_a)(1-4C)alkyl-OR_a, -N(R_a)(1-4C)alkyl-N(R_a)₂, N(R_a)(1-4C)alkyl-N(R_a)-C(R_a)=O, -R_k, -1-4C (fluoro)alkyl mono or di substituted with R_k, -S(O)_n-R_k;

Q³ = T₁, F, Cl, or Br, (1-4C)alkyl-OR_a or (1-4C)alkyl substituted R_k;

Q⁴ = T₁, F, Cl, or Br, 1-6C alkyl-OR_a, -N(R_a)₂, or (1-6C)alkyl-N(R_a)₂;

R¹ and R² = T₁, T₂, -O-(1-4C)alkyl-OR_a, -O(1-4C)alkyl-SR_a, -O(1-4C)alkyl-NH-CO₂R_a, -O(2-4C)alkyl-N(R_a)₂, -S(O)_n(1-4C)alkyl-R_k, -O(1-4C)alkyl-R_k, -O(1-4C)alkyl-O-(1-4C)alkyl-R_k, -O(1-4C)alkyl-SR_k, or (0-4C)alkyl-N(R_a)(R_k);

R³ and R⁴ = T₁, halo, -OH, 1-4C alkyl-OR_a, -O(1-4C)alkyl-OR_a, -O(1-4C)alkyl-SR_a, -O(1-4C)alkyl-NH-CO₂R_a, or -O(2-

4C)alkyl-N(R_a)₂;

R^a = H, 1-4C alkyl;

R^b = H, 1-4C (fluoro)alkyl, -R_k, (1-4C)alkyl-R_k, -S(O)_n-R_k, or -C(=O)R_k;

R^c = H, 1-4C alkyl optionally substituted with -N(R_a)₂, or 1-4C alkyl-phenyl (phenyl is optionally mono- to tri-substituted by halo, 1-4C (fluoro)alkyl, -O(1-4C)(fluoro)alkyl, CN, OH or -S-(1-4C)alkyl);

R^k = P¹, P², P³, P⁴, P⁵, or P⁶;

P¹ = T or T₄;

T₄ = -S-(1-6C)alkyl, phenyloxy (optionally mono- to tri-substituted by halo, 1-6C (fluoro)alkyl or OH), -N(R_a)₂, 1-6C alkyl-N(R_a)₂, -R_k, -(CH₂)_{0.3}C(=O)N(R_a)₂, or (CH₂)_{0.3}C(=O)R_a;

P² = 3-7C cycloalkyl optionally mono- to tri-substituted by T or phenyl;

P³ = 3-7C cycloalkyl fused with a phenyl ring optionally mono - penta substituted by T;

P⁴ = 5 or 6 membered heteroaromatic ring (optionally substituted by T or T₄) containing 1 - 4 heteroatoms O, N, or S;

WO 200236734-A+6

P⁵ = 5 or 6 membered saturated heterocyclic ring (optionally substituted by T, oxo, phenyl, benzyl, phenylethyl, -(CH₂)_{0.3}C(=O)N(R_a), -(CH₂)_{0.3}C(=O)N(R_a)₂, N(R_a)-C(=O)R_a, N(R_a)-C(=O)OR_a, -(CH₂)_{1.3}N(R_a)-C(=O)R_a, -N(R_a)₂, -(CH₂)_{1.3}N(R_a)₂, R_k, -N(R_a)R_k or (CH₂)_{1.3}R_k) containing 1 - 4 heteroatoms;

P⁶ = 8 - 10 membered heteroaromatic ring (optionally substituted by T or =O) containing 1 - 4 heteroatoms O, N, or S;

R_i = 5 or 6 membered optionally saturated heteromonocyclic ring (optionally substituted by halo, oxo, 1-4C alkyl or -O(1-4C)alkyl) containing 1 - 4 N, or naphthyl;

G = N or CH optionally substituted by one of R¹ - R³.

Provided that:

(1) when G is not N and Q¹ - Q⁴ = H, then at least one of R¹ - R³ is not H;

(2) when G is not N, Q¹ is H, Q² is halo or 1-6C alkyl or phenyl (optionally substituted by halo or 1-6C alkyl), or benzyl (optionally substituted by halo or 1-6C alkyl), Q³ and Q⁴ is H and one of R¹ - R³ is H, halo or 1-6C alkyl, then R¹ - R³ is not H, halo, or 1-6C alkyl;

(3) when G is not N, Q¹ - Q⁴ is H and one of R¹ - R³ is -CO₂R_a, then at least one of R¹ - R³ is not H; and

(4) when G is not N and Q¹ - Q⁴ is H, then either Q³ is not substituted by benzyl or at least one of R¹ - R³ is not H.

(189pp8000DwgNo.0/0)

WO 200236734-A/7

2002-362237/39 B03 (B02) ASTR 2000.09.04
 ASTRAZENECA AB *WO 200220484-A1
 2000.09.04 2000-021670(4+2000GB-021670) (2002.03.14) C07D
 211/46, A61K 31/445, C07D 401/12

New piperidine derivatives are modulators of chemokine receptor activity, useful for treating, e.g. asthma, rhinitis or autoimmune, inflammatory, proliferative or immunological diseases (Eng)

C2002-102505 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
 CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
 MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG
 SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA
 ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH
 GM GR IE IT KE LS LU MC MW MZ NL OA PT SD
 SE SL SZ TR TZ UG ZW)

Addnl. Data: SANGANEE H, SPRINGTHORPE B
 2001.08.30 2001WO-SE01869

NOVELTY

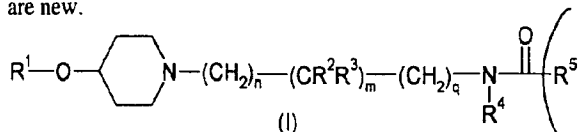
New piperidine derivatives (I) active as modulators of chemokine receptor activity are useful for treating e.g. asthma or rhinitis or

B(6-B1, 6-D1, 6-D2, 6-D3, 6-D7, 6-D9, 7-D5, 14-A1,
 14-A2B1, 14-C1, 14-C3, 14-C6, 14-C9, 14-E8, 14-F7, 14-F9, 14-G2,
 14-G2A, 14-H1, 14-J1A4, 14-J1B3, 14-K1A, 14-K1B, 14-N3, 14-N14,
 14-N17C, 14-S4) .17

autoimmune, inflammatory, proliferative or immunological diseases.

DETAILED DESCRIPTION

Piperidine derivatives of formula (I) and their salts and solvates are new.



R¹ = phenyl (optionally substituted by cyano, S(O)₂(1-6C alkyl), S(O)₂(1-6C haloalkyl), halo, 1-6C alkyl, 1-6C haloalkyl or 1-6C alkoxy);

n = 0-4;

m = 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3; when R² and R³ H or 1-6C alkyl, and R⁴ = H, then R⁵ = a 3-10-

|WO 200220484-A+

reactant: R₅ - C - L →

membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms selected from N, O and S, the ring system being substituted at least once with 1-6C alkyl (substituted with NH₂, CO₂(1-6C alkyl), S(O)₂(1-6C alkyl), NHS(O)₂(1-6C alkyl) or S(O)₂NR¹³R¹⁴), S(O)₂(1-6C alkyl), S(O)₂(1-6C hydroxyalkyl), S(O)₂NH(1-6C alkyl), NHC(O)(1-6C alkyl), NHS(O)₂(1-6C alkyl), 1-6C alkoxy (substituted with 1-6C alkoxy, OH, CO₂(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH₂), 2-6C alkenyl, pyrrolyl and δ³-pyrrolinyl; and optionally further substituted with halo, cyano, nitro, OH, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkoxy carbonyl, 1-6C haloalkyl, 1-6C haloalkoxy, NR⁶R⁷, 3-6C cycloalkylamino, 1-6C alkylthio, 1-6C alkylthio(1-6C alkyl), 1-6C alkylcarbonylamino, C(O)NR⁸R⁹, sulfonamido (S(O)₂NH₂), (di)1-6C alkylsulfonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl and C(O)R¹⁰-substituted 1-6C alkyl or 1-6C alkoxy; when R² and R³ H or 1-6C alkyl and R⁴ = 1-4C alkyl or 3-6C cycloalkyl(1-4C alkyl), then R⁵ = a 3-10-membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms selected from N, O and S, the ring system being

optionally substituted by halo, cyano, nitro, OH, 1-6C alkyl (optionally substituted with halo, 1-6C alkylthio, NH₂, C(O)R¹⁰, CO₂(1-6C alkyl), S(O)₂(1-6C alkyl), NHS(O)₂(1-6C alkyl) or S(O)₂NR¹³R¹⁴), 3-6C cycloalkyl, 1-6C alkoxy (substituted with halo, 1-6C alkoxy, OH, C(O)R¹⁰, CO₂(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH₂), 2-6C alkenyl, 1-6C alkoxy carbonyl, NR⁶R⁷, 3-6C cycloalkylamino, 1-6C alkylthio, 1-6C alkylcarbonylamino, C(O)NR⁸R⁹, sulfonamido (S(O)₂NH₂), (di)1-6C alkylsulfonamido, S(O)₂(1-6C alkyl), S(O)₂(1-6C hydroxyalkyl), S(O)₂NH(1-6C alkyl), NHC(O)(1-6C alkyl), NHS(O)₂(1-6C alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or δ³-pyrrolinyl; and when R² = phenyl (optionally substituted with halo, 1-4C alkyl or 1-4C alkoxy), R³ = H or 1-6C alkyl, and R⁴ = H, 1-4C alkyl or 3-6C cycloalkyl(1-4C alkyl), then R⁵ = a 3-10-membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms selected from N, O and S, the ring system being optionally substituted by halo, cyano, nitro, OH, 1-6C alkyl (optionally substituted with halo, 1-6C alkylthio, NH₂, C(O)R¹⁰, CO₂(1-6C alkyl), S(O)₂(1-6C alkyl), NHS(O)₂(1-6C alkyl) or

|WO 200220484-A+1

2002-362237/39

S(O)₂NR¹³R¹⁴), 3-6C cycloalkyl, 1-6C alkoxy (substituted with halogen, 1-6C alkoxy, OH, C(O)R¹⁰, CO₂(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH₂), 2-6C alkenyl, 1-6C alkoxy carbonyl, NR⁶R⁷, 3-6C cycloalkylamino, 1-6C alkylthio 1-6C alkylcarbonylamino, C(O)NR⁸R⁹, sulfonamido (S(O)₂NH₂), (di)1-6C alkylsulfonamido, S(O)₂(1-6C alkyl), S(O)₂(1-6C hydroxyalkyl), S(O)₂NH(1-6C alkyl), NHC(O)(1-6C alkyl), NHS(O)₂(1-6C alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or δ³-pyrrolinyl; R¹⁰ = OH or NR¹¹R¹²; and R⁶-R⁹ and R¹¹-R¹⁴ = H or 1-6C alkyl; provided that n+m+q = 1, 2, 3 or 4.

INDEPENDENT CLAIMS are also included for:

(1) the preparation of (I); and

(2) use of (I) in the manufacture of a medicament.

ACTIVITY

Antiasthmatic; Antiallergic; Antiinflammatory; Immunosuppressive; Cytostatic; Anti-HIV; Virucide; Antitussive; Antiarthritic; Antirheumatic; Ophthalmological; Antipsoriatic;

Dermatological; Antiulcer; Antimigraine; Analgesic; Neuroprotective; Nootropic; Antiarteriosclerotic; Thyromimetic; Antidiabetic; Nephrotropic; Antileprotic; Antibacterial; Hemostatic; Gynecological.

MECHANISM OF ACTION

Modulators of chemokine receptor (especially CCR3) activity; H1 antagonists.

Test details are described but no results are given.

USE

The compounds can be used to treat a CCR3 mediated disease state e.g. asthma or rhinitis (claimed). They can be used to treat asthma (e.g. allergic or dust asthma), or rhinitis (e.g. acute or chronic rhinitis, e.g. rhinitis caseosa, membranous rhinitis including croupous or vasomotor rhinitis). They can also be used for treating e.g. autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and AIDS). The compounds are also H1 antagonists and may be used in the treatment of allergic disorders.

|WO 200220484-A+2

(con't)

They can be used to treat respiratory tract obstructive disease of airways e.g. chronic obstructive pulmonary disease (COPD), bronchitis, sarcoidosis, farmer's lung and related diseases, nasal polypsis, fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough; (bone and joints) arthrides e.g. rheumatic, infectious, autoimmune, spondyloarthropathies (e.g. ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis; (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, pemphigus, bullous pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata or vernal conjunctivitis; (gastrointestinal tract) Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (e.g. migraine, rhinitis or eczema); allograft rejection, acute and chronic following e.g. transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea, or chronic graft versus host disease; and/or other tissues or diseases such as Alzheimer's disease, multiple sclerosis, atherosclerosis, AIDS, lupus disorders (such as systemic lupus), erythematosis, Hashimoto's thyroiditis, myasthenia

gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (e.g. lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

ADMINISTRATION

(I) can be used in doses of e.g. 0.01-100, (preferably 0.1-20) mg/kg/ay by e.g. oral, parenteral or topical routes.

EXAMPLE

2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylamine (0.20 g) was dissolved in dichloromethane (4 ml). 3-[(Methylsulfonyl)methyl]benzoic acid (see WO00/15609; or by hydrolysis of methyl 3-[(methylsulfonyl)methyl]benzoate, 0.132 g) triethylamine (0.289 ml) and PyBrop (RTM, 0.483 g) were added. After 24 hours at room temperature sodium hydrogen carbonate (aqueous) was added and the product extracted with diethyl ether. The organics were dried and concentrated. Purification by reverse phase high pressure liquid chromatography (with a gradient eluent system (25% acetonitrile/NH₄OAc (aqueous, 0.1%) to 95% acetonitrile/NH₄OAc (aqueous, 0.1%) (any excess NH₄OAc was

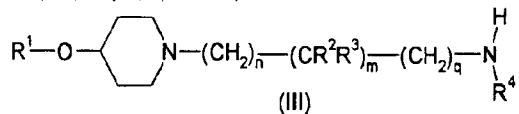
WO 200220484-A+/3

2002-362237/39

removed by dissolving the compound in dichloromethane and washing with aqueous saturated sodium hydrogen carbonate followed by drying of the organics with magnesium sulfate and evaporation of solvent) gave N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-3-[(methylsulfonyl)methyl]benzamide (0.101 g, m. pt. 112-114 °C).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) may be prepared by reacting a piperidine compound of formula (III) with a compound of formula LC(=O)R⁵ (IV), (claimed).



L = a leaving group.
(70pp1703DwgNo.0/0)

WO 200220484-A/4

2000-647331/62 B02 NEUR- 1999.04.02
NEUROGEN CORP *WO 200059888-A1
1999.04.02 1999-285420(+1999US-127624) (2000.10.12) C07D
235/14, A61K 31/4045, 31/4184, G01N 33/50, A61P 25/00, C07D 209/14
New N-benzimidazolylmethyl and N-indolylmethyl benzamide
derivatives, useful as corticotropin releasing factor (CRF)
modulators for treating e.g. depression, anxiety, cardiovascular
and eating disorders (Eng)

C2000-195862 N(AE AL AM AT AU AZ BA BB BG BR BY CA CH
CN CR CU CZ DE DK DM EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY
DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU
MC MW NL OA PT SD SE SL SZ TZ UG ZW)

Addnl. Data: HORVATH R F, GE P, YOON T, HUTCHISON A
2000.03.31 2000WO-US08570, 1999.04.02 1999US-285420

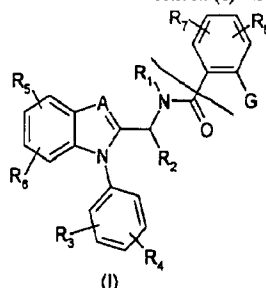
NOVELTY

N-benzimidazolylmethyl and N-indolylmethyl benzamide
derivatives (I) are new.

B(4-E5, 6-D1, 6-D5, 12-K4F, 14-E11, 14-E12, 14-F1,
14-J1A1, 14-J1B4) .7

DETAILED DESCRIPTION

N-benzimidazolylmethyl and N-indolylmethyl benzamide
derivatives of formula (I) and their salts are new.



reactant

(I)
A = N or CY;

Y = H or 1-6C alkyl;

R1 = H, 1-6C alkyl or hydroxy 1-6C alkyl;

R2 = H or 1-6C alkyl, provided R2 is H when A is CY;

WO 200059888-A+

G, R3, R4 = H, halo, CF3, OCF3, CN, 1-6C alkyl, 1-6C alkoxy, OH,
hydroxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, SH, 1-6C
alkylthio, thio 1-6C alkyl or 1-6C alkylthio 1-6C alkyl; and
R5- R8 = H, halo, CF3, OCF3, CN, 1-6C alkyl, 1-6C alkoxy, OH, SH, 1-
6C alkoxy 1-6C alkoxy, hydroxy 1-6C alkoxy, hydroxy 1-
6C alkyl, 1-6C alkoxy 1-6C alkyl, amino, mono- or
dialkylamino, 1-6C alkylthio, thio 1-6C alkyl or 1-6C
alkylthio 1-6C alkyl.

INDEPENDENT CLAIMS are included for:

- (1) a packaged pharmaceutical composition comprising (I), a container
and instructions;
- (2) a method of localizing CRF receptors in tissue section samples by
contacting the sample with labelled (I) and binding, washing the
sample to remove unbound compound, and detecting the bound
compound; and
- (3) preparation of (I).

ACTIVITY

Tranquilizer; antidepressant; cardiant, anorectic; anabolic;
nootropic; neuroprotective; antiparkinsonian; anticonvulsant; anti-
HIV; vasotropic; vulnerary; antiaddictive; analgesic.

MECHANISM OF ACTION

CRF receptor modulator.

In a standard assay of CRF binding, the compounds (I) exhibit an IC50
value of less than 1 micro M, preferably less than 100, especially less
than 10 nM (claimed).

USE

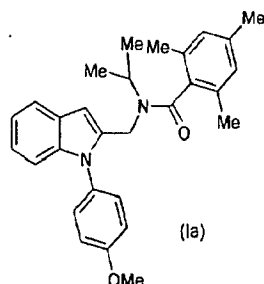
(I) is used to treat stress, anxiety, depression, cardiovascular
disorders, obesity and eating disorders, drug addiction, obsessive-
compulsive disorders, stress, neurological disorders such as
supranuclear palsy, AIDS related dementia, multi infarct dementia,
Alzheimer's disease, Huntingdon's disease and Parkinson's disease,
ischemia, trauma, fibromyalgia and epilepsy. (I) can also be used as a
probe, for localizing CRF receptors, inhibiting binding of CRF to the
CRF1 receptor in IMR32 cells, and for altering the signal-transducing
activity of a cell surface CRF1 receptor (all claimed).

SPECIFIC COMPOUNDS

68 compounds (I) are specifically claimed, e.g. N-[[1-(4-
methoxyphenyl)indol-2-yl]methyl]-N-(methylethyl)(2,4,6-
trimethylphenyl)carboxamide (Ia).

WO 200059888-A+/1

2000-647331/62



ADMINISTRATION

0.1-140 (preferably 0.5-7) mg/kg/day e.g. orally, topically,
parenterally, rectally or by inhalation.

EXAMPLE

(2-aminophenyl)(4-methoxy-2-methylphenyl)amine (60 g) in
chloroform (350 ml) was stirred with imidate (59 g) at room
temperature for one hour. NaHCO3 (100 ml) was added, and extracted

with dichloromethane (4x150 ml), dried (Na2SO4), and the solvent
was removed *in vacuo*. The residue was purified by silica gel
chromatography to give 1-[2-(chloromethyl)benzimidazolyl]-4-
methoxy-2-methylbenzene (IIa) (50 g, 65%). (IIa) (3 g) in acetonitrile
(20 ml) was reacted with isopropylamine (5 ml) at 50°C in a sealed
tube for one hour. Solvent was removed *in vacuo*, and the residue
partitioned between ethyl acetate (30 ml) and 1N NaOH solution (10
ml). The organic layer was dried (Na2SO4) to give [[1-(4-methoxy-2-
methylphenyl)benzimidazol-2-yl]methyl](methylethyl)amine (3.1 g,
98%). This amine was stirred with 2,4,6-trimethylbenzoylchloride (2.6
ml) in 1:1 dichloromethane:NaHCO3 solution (30 ml) for one hour at
room temperature. The mixture was partitioned, the organic layer
dried, and the solvent removed *in vacuo*. The crystallized product was
titrated with ether, filtered and dried to give N-[[1-(4-methoxy-2-
methylphenyl)benzimidazol-2-yl]methyl]-N-(methylethyl)(2,4,6-
trimethylphenyl)carboxamide (Ia) (4.4 g, 92%).

DEFINITIONS

Preferred Definitions :

WO 200059888-A+/2

(con't)

(C) 2004 Copyright Derwent Information Ltd.

R_1 = isopropyl;

R_2 = H;

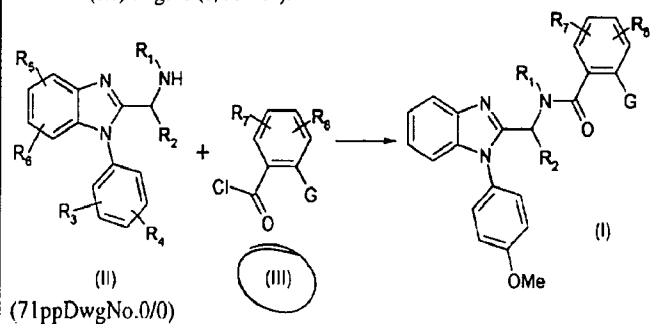
Q = trimethylphenyl;

R_3, R_6 = H, F, Cl, OH, CF_3 or Me;

provided that R_3 and R_4 can not both be H.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) is prepared by e.g. reacting a benzimidazole compound of formula (II) with a benzoyl chloride of formula (III) to give (I; A = N).



WO 200059888-A/3

<p>2000-526517/48 B03 MERI 1999.03.02 MERCK SHARP & DOHME LTD *GB 2347423-A 1999.03.02 1999-004786(+1999GB-004786) (2000.09.06) C07D 211/20, A61K 31/445 // A61P 25/00 (A61P 29/00) New piperidine derivatives, useful for treatment of e.g. pain, inflammation, migraine, emesis and post-herpetic neuralgia, are tachykinin and particularly substance P antagonists C2000-156553 Addnl. Data: MACLEOD A M, SWAIN C J, VAN NIEL M B 2000.02.22 2000GB-004167</p>	<p>B(6-H, 7-D5, 14-C1, 14-C3, 14-C9, 14-E1, 14-E5, 14-E8, 14-E10, 14-E10C, 14-E11, 14-F1B, 14-F2, 14-G2A, 14-G2C, 14-H1, 14-J1A1, 14-J1A3, 14-J1A4, 14-J1B3, 14-J1B4, 14-J5, 14-J7, 14-K1, 14-K1A, 14-L6, 14-M1, 14-N3, 14-N7B, 14-N16, 14-N17, 14-N17A, 14-S1) .13</p> <p>reactant (iv) (ii)</p> <p>$R_1, R_2 =$ phenyl (optionally substituted by 1-3 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-7C cycloalkyl, (3-7C cycloalkyl)(1-4C alkyl), 3-7C cycloalkoxy, 1-6C fluoroalkyl, 1-6C alkoxy, 1-6C fluoroalkoxy, OH, 1-6C hydroxyalkyl, 1-6C hydroxyalkoxy, SR_a, SOR_a, SO_2R_a, NR_aR_b, NR_aCOR_b, $NR_aCO_2R_b$, COR_a, CO_2R_a, $CONR_aR_b$, adamantyl, morpholinyl (optionally substituted by 1 or 2 1-4C alkyl) or phenyl, phenoxy, phenylazo, benzyl or benzyloxy (all optionally ring-substituted by one or two halogen, 1-4C alkyl, 1-4C alkoxy or OH); or R_3+R_3 on adjacent C = OCH_2O, OCH_2CH_2O, $CH_2CH_2CH_2$, $CH_2CH=CH$, $NR_aCH=CH$ or $OC(R_a)_2CH_2CO$; $R_4-R_7 =$ H or 1-6C alkyl; $R_a, R_b =$ H, 1-6C alkyl, phenyl or CF_3; A = O or S; $B_1 =$ O, S, NR_a or CHR_a; and n = 0-5. An INDEPENDENT CLAIM is included for the preparation of (I).</p> <p>GB 2347423-A+</p>
---	---

<p>$SOR_a, SO_2R_a, NR_aR_b, NR_aCOR_b, NR_aCO_2R_b, COR_a, CO_2R_a$, or $CONR_aR_b$; $R_3 =$ halogen, CN, NO_2, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-7C cycloalkyl, (3-7C cycloalkyl)(1-4C alkyl), 3-7C cycloalkoxy, 1-6C fluoroalkyl, 1-6C alkoxy, 1-6C fluoroalkoxy, OH, 1-6C hydroxyalkyl, 1-6C hydroxyalkoxy, $SR_a, SOR_a, SO_2R_a, NR_aR_b, NR_aCOR_b, NR_aCO_2R_b, COR_a, CO_2R_a, CONR_aR_b$, adamantyl, morpholinyl (optionally substituted by 1 or 2 1-4C alkyl) or phenyl, phenoxy, phenylazo, benzyl or benzyloxy (all optionally ring-substituted by one or two halogen, 1-4C alkyl, 1-4C alkoxy or OH); or R_3+R_3 on adjacent C = OCH_2O, OCH_2CH_2O, $CH_2CH_2CH_2$, $CH_2CH=CH$, $NR_aCH=CH$ or $OC(R_a)_2CH_2CO$; $R_4-R_7 =$ H or 1-6C alkyl; $R_a, R_b =$ H, 1-6C alkyl, phenyl or CF_3; A = O or S; $B_1 =$ O, S, NR_a or CHR_a; and n = 0-5. An INDEPENDENT CLAIM is included for the preparation of (I).</p> <p>ACTIVITY Analgesic; antiinflammatory; antimigraine; antiemetic;</p>	<p>antidepressant; eating disorders; antiasthmatic; antiarthritic; osteopathic; antirheumatic; vulnerary; tranquilizer; neuroleptic; nootropic; antiparkinsonian; antimicrobial; neuroprotective; muscular; antiaddictive; antialcoholic; antismoking; endocrine; anticonvulsant; vasotropic; cerebroprotective; respiratory; gastrointestinal; antipsoriatic; antiallergic; cytostatic; ophthalmological; antiulcer; antacid; immunosuppressive; dermatological; uropathic; antianginal</p> <p>MECHANISM OF ACTION Tachykinin antagonist; Substance P antagonist; mucolytic. CHO cells stably expressing the human NK-1 receptor were incubated with (I) and [^{125}I]-Tyr⁸-substance P at room temperature until equilibrium is achieved and the receptor-ligand complexes and then harvested by filtration on GF/C filters soaked in polyethyleneimine. (I) showed IC_{50} of < 100 nM, preferably < 10 nM.</p> <p>USE For treatment of a disorder associated with an excess of tachykinins, particularly pain, inflammation, migraine, emesis or post-herpetic neuralgia (claimed). Also for treatment of depression, dysthymic disorders, depressive neuroses, anorexia, seasonal affective</p> <p>GB 2347423-A+/1</p>
---	---

<p>2000-526517/48</p> <p>disorder, asthma, osteoarthritis, rheumatoid arthritis, burns, anxiety disorders, schizophrenia, delirium, dementia, amnesia, Alzheimer's disease, Parkinson's disease, Creutzfeld-Jakob disease, movement disorders, substance related disorders due to drugs, alcohol and nicotine such as dependence and withdrawal, psychotic disorders, sleep disorders, sexual dysfunction, epilepsy, Down's syndrome, demyelinating diseases, cerebral vascular disorders, respiratory disorders, cystic fibrosis, inflammatory bowel disease, psoriasis, allergies, hypersensitivity disorders, ophthalmic disorders, cancer, gastric disorders, gastritis, ulcers, acid indigestion, dyspepsia, transplant rejection, systemic lupus erythematosus, scleroderma, cystitis, angina and Raynaud's disease.</p> <p>ADVANTAGE Strongly inhibitory for tachykinins without the side effects of prior art drugs such as benzodiazepines.</p> <p>SPECIFIC COMPOUNDS Ten compounds are specifically claimed, e.g. 3-(3-acetamidophenoxy)-1-[4-phenyl-4-(3,5-bis-trifluoromethyl-</p>	<p>benzyloxymethyl)piperidine]-propan-2-ol of formula (Ia).</p> <p>(Ia)</p> <p>ADMINISTRATION Dosage is 0.001-50 (0.05-10) mg/kg/day. Administration is oral, parenteral, nasal, sublingual or rectal or by inhalation or insufflation.</p> <p>EXAMPLE</p> <p>GB 2347423-A+/2</p>
--	--

(con't)

3-Ethylphenol (1.50 g) was dissolved in 1N sodium hydroxide and epichlorohydrin (2.07 g) added and the mixture stirred at room temperature for 4 days. Excess epichlorohydrin was removed by concentration *in vacuo* and the two phase mixture treated with tetrahydrofuran (10 ml) and 1N sodium hydroxide (10 ml). The mixture was heated to 55 °C for 15 minutes and then stirred at room temperature for 30 minutes, followed by removal of tetrahydrofuran by *in vacuo* concentration. The product was extracted with ethyl acetate (2 × 50 ml), concentrated *in vacuo* and purified by flash column chromatography on silica (using 150:10:1 dichloromethane:methanol:ammonia as eluant) to give 3-ethylphenoxy-oxirane as a yellow oil.

Of this product, 200 mg was dissolved in isopropanol (10 ml) and refluxed with 4-phenyl-4-[3,5-bis-(trifluoromethyl)-benzyloxymethyl]piperidine (375 mg) for 16 hours. The mixture was concentrated *in vacuo* to a yellow oil which was purified by flash column chromatography on silica using the same elution mixture as the previous step to give 3-ethylphenoxy-1-[4-phenyl-4-[3,5-bis-(trifluoromethyl)-benzyloxymethyl]piperidine]propan-2-ol as a yellow oil.

This product could be optionally converted to the oxalate salt by dissolution in diethyl ether and addition of 1 equivalent of oxalic acid.

DEFINITIONS

Preferred Definitions:

A, B₁ = O; and

R₄-R₇ = H.

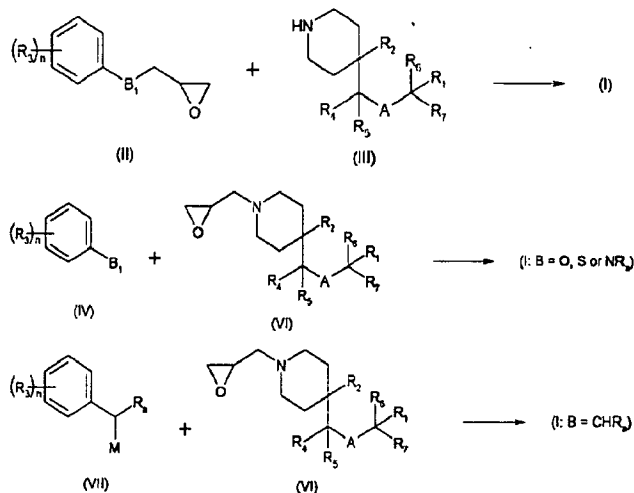
TECHNOLOGY FOCUS

Organic Chemistry - Preparation; Claimed preparation of (I) is by one of 3 methods, i.e.:

- (A) by reaction of an epoxide of formula (II) with a 4,4-disubstituted piperidine derivative of formula (III);
- (B) for (I) where B is other than CHR₃, by reaction of phenyl derivative of formula (IV) with an 1-epoxymethylpiperidine derivative of formula (VI) in the presence of a base; or
- (C) for (I) where B = CHR₃, by reaction of an 1-epoxymethylpiperidine derivative of formula (VI) as above with an organometallic benzyl derivative of formula (VII).

GB 2347423-A+/3

2000-526517/48



M = Li or MgHal; and

Hal = Cl, Br or I.

Each of the above processes may be followed by one or more of removal of any protecting groups, optical resolution and/or conversion to salt form

(S6ppDwgNo.0/0)

GB 2347423-A/4

2000-442131/38 C02 BADI 1998.12.04
 BASF AG *WO 200034247-A2
 1998.12.04 1998-1055850(+1998DE-1055850) (2000.06.15) C07D
 231/00

Preparation of new or known 1-unsubstituted 4-benzoyl-pyrazole derivatives useful as pre- or post-emergence, total or selective herbicides, from 1-substituted analog and acid (Ger)

C2000-134336 N(AE AL AM AT AU AZ BA BB BG BR BY CA CH
 CN CR CU CZ DE DK DM EE ES FI GB GD GE GH
 GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
 LR LS LT LU LV MA MD MG MK MN MW MX NO
 NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
 TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY
 DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU
 MC MW NL OA PT SD SE SL SZ TZ UG ZW)

Addnl. Data: NEIDLEIN U, GOETZ N, MISSLITZ U, BAUMANN E,
 VON DEYN W, KUDIS S, LANGEMANN K, MAYER G,
 WITSCHEL M, OTTEN M, WESTPHALEN K, WALTER
 H
 1999.12.01 1999WO-EP09343

NOVELTY

C(7-D8, 14-VI, 14-V2B) .2

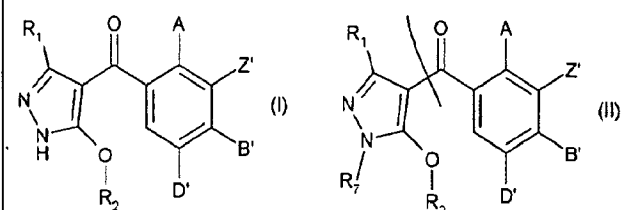
Preparation of 1-unsubstituted 4-benzoyl-5-oxy-pyrazoles (I) involves treating a 1-(branched alkyl, alkenyl or alkynyl or benzyl)-substituted analog (II) with acid to cause elimination of an olefin or alcohol.

DETAILED DESCRIPTION

Preparation of 1-unsubstituted 4-benzoyl-pyrazoles of formula (I) involves treating a 1-substituted analog of formula (II) with an inorganic or organic acid at pH less than 2, to cause elimination of an olefin or alcohol.

reactant (iv)

WO 200034247-A+



R₁ = H or T';
 R₂ = H, alkyl, alkenyl, alkynyl, benzyl, benzoyl, C(O)OT'', -T''-C(O)OH, -T''-C(O)OT'', SO₂T'' or SO₂-phenyl (all optionally substituted (os) by T'', OT'', ST'', halogen, OH, NH₂, NO₂ or CN);
 T'' = 1-4C alkyl;
 T' = T or 1-4C haloalkyl;
 A, B', D' = alkyl, alkenyl, alkyl or OT'' (all os by halogen, OH, OT'' or CN) or H, halogen, OH, CN, NO₂, -(Y')_n-S(O)_mR₃ or -(Y')_n-C(O)R₄;
 Z' = as for A, phenyl (os by T', halogen, OH, CN or NO₂) or a 5- or 6-membered saturated or unsaturated heterocycle containing 1 - 3 of O, S and N (os by halogen, CN, NO₂, -C(O)R₄, T', 3-8C

cycloalkyl, OT', ST', N(T'')₂, phenyl (itself os by halogen, CN, NO₂ or T') or oxo (optionally as the hydroxy tautomer) and optionally fused with a phenyl ring (os by halogen, CN, NO₂ or T'), a carbocycle or a second heterocycle (os by halogen, CN, NO₂, T', N(T'')₂ or OT') to form a bicyclic system);

Y' = O or NR₅;

n = 0 or 1;

m = 0 - 2;

R₃ = T' or NR₅R₆;

R₄ = OH, T', OT'' or NR₅R₆;

R₅ = H or T'';

R₆ = T'';

R₇ = branched 3-12C alkyl, 3-12C alkenyl or 4-12C alkynyl (os by halogen or OT'') or benzyl (os by halogen, CN, NO₂, 1-4C haloalkyl, SO₂T'' or C(O)T'');
 An INDEPENDENT CLAIM is included for (I) and their salts as new compounds, provided that Z' is other than 5-isoxazolyl or 5-pyrazolyl.

ACTIVITY

Herbicidal. 4-(3-(4,5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methylbenzoyl)-5-(2,4-difluorobenzoyloxy)-1H-pyrazole (Ia) at 0.125

WO 200034247-A+I

2000-442131/38

kg/ha post-emergence showed excellent herbicidal activity (no quantitative results given) against weeds such as *Chenopodium album*, *Echinochloa crus-galli* and *Setaria viridis*.

MECHANISM OF ACTION

None given.

USE

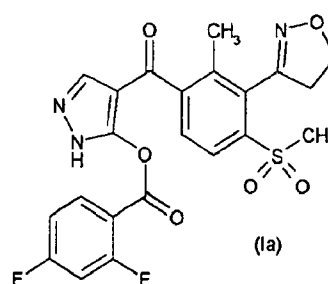
(I) are herbicides (claimed for the new compounds (I)). They are useful as total herbicides or (at lower application rates) selective herbicides for controlling grasses and other weeds in crops such as wheat, rice, maize, soya and cotton.

ADVANTAGE

The process gives (I) in high yield.

SPECIFIC COMPOUNDS

9 Compounds (I) are disclosed, e.g. 4-(3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methylbenzoyl)-5-(2,4-difluorobenzoyloxy)-1H-pyrazole of formula (Ia).



ADMINISTRATION

Application rate is 0.001 - 3 (preferably 0.01 - 1) kg/ha, pre- or post-emergence.

EXAMPLE

A solution of 3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-

WO 200034247-A+2

(con't)

(C) 2004 Copyright Derwent Information Ltd.

methylbenzoyl chloride (1.0 g) in dioxan was treated with N-tert-butyl-pyrazolone (0.61 g) and dicyclohexyl carbodiimide (0.79 g), stirred overnight at room temperature, filtered, treated with potassium carbonate (0.58 g), heated at reflux for 3 hours and evaporated. The residue was worked up to give 2-tert-butyl-2H-pyrazol-3-yl 3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methylbenzoate (0.81 g; 57 %). A solution of the above product (0.5 g) in acetonitrile (10 ml) was treated with trifluoromethanesulfonic acid (0.37 g), heated at reflux for 5 hours and evaporated. The residue was worked up to give 4-(3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methylbenzoyl)-5-hydroxy-1H-pyrazole (0.27 g; 54 %).

DEFINITIONS

Preferred Definitions:

Unless specified otherwise alkyl groups are 1-6C and alkenyl or alkynyl groups are 2-6C.

In the new compounds:

Z' = oxazolyl, 3- or 4-isoxazolyl, thiazolyl, isothiazolyl, 3- or 4-pyrazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolinyl, oxazoliny, isoxazoliny, thiazoliny, isothiazoliny, pyrazoliny, imidazoliny or dioxolany;

R₁, R₂ = H or T'';

A, B', D' = H, T', OT'', ST'', SO₂T'', halogen, OH, CN or NO₂.

In the process:

R₇ = α-branched 3-6C alkyl or benzyl (os in the 4-position by Cl, CN, NO₂, CF₃, SO₂CH₃ or acyl).

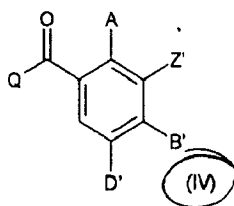
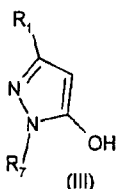
TECHNOLOGY FOCUS

Organic Chemistry - Preferred Process: The organic acid is trifluoromethanesulfonic or trichloroacetic acid; and the inorganic acid is sulfuric, nitric, hydrochloric or hydrobromic acid. Reaction is carried out in a solvent, specifically acetonitrile, dimethyl formamide, dioxan, tetrahydrofuran, toluene or chlorobenzene.

(II) are prepared by acylating hydroxy-pyrazoles of formula (III) with benzoyl halides of formula (IV), followed by catalytic rearrangement of the acylation product.

WO 200034247-A+3

2000-442131/38



Q = halogen.

(177pp2400DwgNo.0/0)

WO 200034247-A/4

2000-423357/36 B03 (B02) AMHP 1998.12.09
AMERICAN HOME PROD CORP *WO 200034269-A1

1998.12.09 1998-208540(+1998US-208540) (2000.06.15) C07D
405/12, A61K 31/33, A61P 31/12, C07D 417/12, 213/75, 213/81

Novel thiourea derivatives useful for treating diseases associated with herpes viruses (Eng)

C2000-128176 N(AE AL AM AT AU AZ BA BB BG BR BY CA CH
CN CR CU CZ DE DK DM EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG UZ VN YU ZA ZW) R(AT BE CH CY DE
DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
MW NL OA PT SD SE SL SZ TZ UG ZW)

Addnl. Data: BLOOM J D, DIGRANDI M J, DUSHIN R G, LANG S A,
O'HARA B M
1999.12.06 1999WO-US28892

NOVELTY

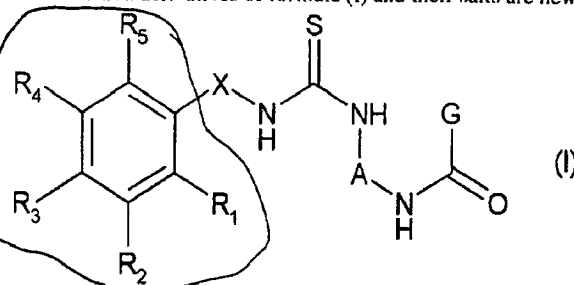
Thiourea derivatives (I) are new.

reactant II

DETAILED DESCRIPTION

B(6-H, 7-H, 14-A2A3) .3

Thiourea derivatives of formula (I) and their salts are new.



R₁-R₅ = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C perhaloalkyl,
3-10C cycloalkyl, 3-10C heterocycloalkyl, aryl, heteroaryl,
halo, CN, NO₂, CO₂R₆, COR₆, OR₆, SR₆, SOR₆, SO₂R₆,
CONR₇R₈, NR₆NR₇R₈, NR₇R₈ or W-Y-(CH₂)_n-Z; or
R₂+R₃ or R₃+R₄ = 3-7 membered heterocycloalkyl or heteroaryl;
R₆, R₇ = H, 1-6C alkyl, 1-6C perhaloalkyl or aryl;
R₈ = H, 1-6C alkyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C
WO 200034269-A+

heterocycloalkyl, aryl or heteroaryl; or

R₇+R₈ = 3-7 membered heterocycloalkyl;

A = heteroaryl;

W = O, NR₆ or is absent;

Y = CO or CO₂ or is absent;

Z = 1-4C alkyl, CN, CO₂R₆, COR₆, CONR₇R₈, OCOR₆, NR₆COR₇,
OCONR₆, OR₆, SR₆, SOR₆, SO₂R₆, SR₆NR₇R₈ (sic), NR₇R₈ or
phenyl;

G = aryl or heteroaryl;

X = bond, NH, 1-6C alkyl, 2-6C alkenyl, 1-6C alkoxy, 1-6C thioalkyl,
1-6C alkylamino or CH₂;

J = 1-6C alkyl, 3-7C cycloalkyl, phenyl or benzyl; and
n = 1-6.

ACTIVITY

Virucide. In a V2V antiviral (ELISA) assay N-[2-(5-chloro-2,4-
dimethoxy-phenyl)-thioureido]-pyridin-3-yl]-2-fluorobenzamide
inhibited viral replication by 90% at a concentration of 10 micro g/ml.

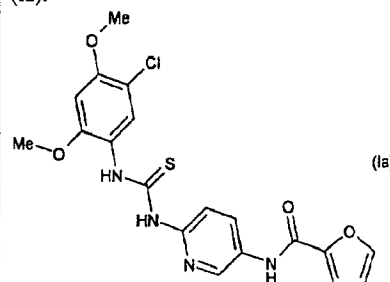
USE

(I) are useful for inhibiting the replication of a herpes virus and
treating herpes virus infections such as human cytomegalovirus,

herpes simplex virus, and varicella zoster virus (claimed). (I) are also
useful for inhibiting and/or treating diseases associated with herpes
viruses including Epstein-Barr virus, human herpes viruses-6 and -7,
and Kaposi herpes virus.

SPECIFIC COMPOUNDS

31 Compounds (I) are claimed e.g. furan 2-carboxylic acid {6-[3-
(5-chloro-2,4-dimethoxy-phenyl)-thioureido]-pyridin-3-yl]-amide
(Ia).



WO 200034269-A+1

2000-423357/36

ADMINISTRATION

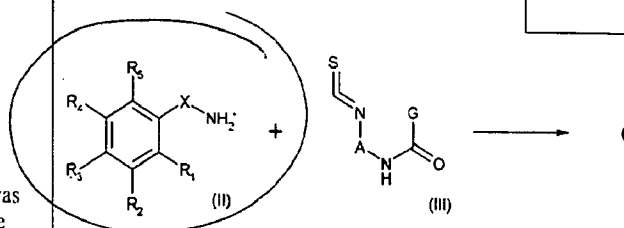
Dosage is 0.01-1000 mg/kg/day orally or 0.1-100 mg/kg/day
parenterally.

EXAMPLE

To a solution of 2,5-dichloroaniline (0.16 g) in THF (20 ml) was
added freshly prepared 1,1'-thiocarbonyldiimidazole (0.2 g) and the
mixture was stirred for 30 minutes at room temperature. [1,2,3]-
Thiadiazole-4-carboxylic acid (4-amino-phenyl) amide (0.22 g) was
added and the mixture was stirred for 6 hours. Work up gave [1,2,3]-
thiadiazole-4-carboxylic acid {4-[3-(2,5-dichlorophenyl)-thioureido]-
phenyl}-amide.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) can be prepared by reacting
appropriately substituted amines of formula (II) with appropriately
substituted isothiocyanates of formula (III).

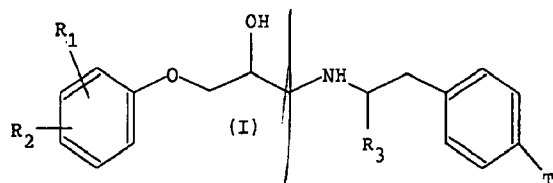


(162pp1894DwgNo.0/0)

WO 200034269-A/2

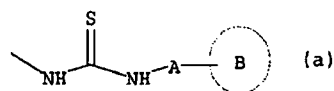
New thiourea derivatives - are beta-3 receptor agonists which accelerate insulin secretion and elevate insulin sensitivity, useful for treating diabetes
 C98-041612

Thiourea derivatives of formula (I) and their salts are new.



T = a group of formula (a):

B(10-A13B, 14-S4) .2



R₁, R₂ = H, halo, hydroxyl, cyano, nitro, trifluoromethyl, lower alkoxy, lower acylamino, lower alkylsulphonylamino, lower alkoxy-carbonylamino, N'-lower alkylureido or lower alkyl (optionally substituted);

R₃ = H or lower alkyl;

A = a bond, lower alkylene or lower alkenylene; and ring B = optionally substituted aryl or cycloalkyl.

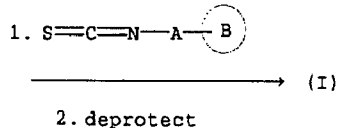
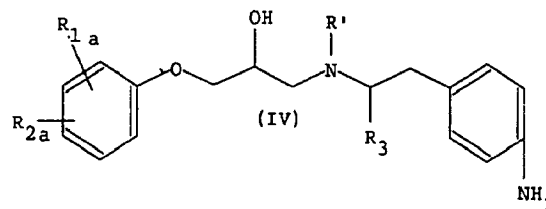
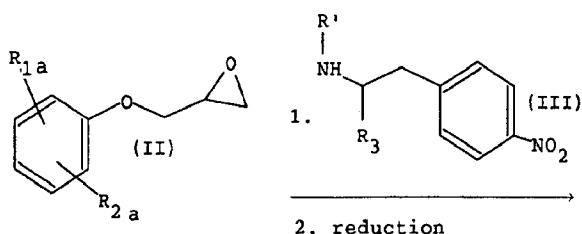
USE

(I) are β-3 receptor agonists and are useful for treating diabetes.
 (I) accelerate insulin secretion and elevate insulin sensitivity.

JP 10007647-A+

PREPARATION

E.g.



R_{1a}, R_{2a} = protecting group for R₁, R₂ and OH; and R' = amino protecting group.

EXAMPLE

(S)-1-[4-[2-[N-t-Butoxycarbonyl-N-(2-hydroxy-3-

JP 10007647-A+/1

98-126135/12

phenoxypropyl)amino]ethyl]phenyl]-3-phenylthiourea (0.33 g) dissolved in methanol (10 ml) and 4 N hydrogen chloride ethyl acetate solution (10 ml) were mixed and stirred at room temperature for 1 hour to give 0.17 g (S)-1-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]phenyl]-3-phenylthiourea (Ia).HCl, m.pt. 214-217 °C. (MHG)
 (20pp002DwgNo.0/0)

JP 10007647-A/2

<p>97-526074/48 C02 (C01) BADI 96.03.27 BASF AG *WO 9735845-A1 96.03.27 96DE-1012032 (97.10.02) C07D 239/54, A01N 43/54, C07C 271/22, 275/24 New 1-methyl-3-benzyl-6-haloalkyl-uracil derivatives - useful as pre- or post-emergence, total or selective herbicides and as desiccants or defoliants, especially for cotton (Ger) C97-167275 N(AU BG BR BY CA CN CZ GE HU IL JP KR KZ LV MX NO NZ PL RO RU SG SI SK TR UA US UZ VN) R(AT BE CH DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE) Addnl. Data: MENKE O, HAMPRECHT G, HEISTRACHER E, KLINTZ R, SCHAEFER P, ZAGAR C, MENGES M, WESTPHALEN K, WALTER H, MISSLITZ U 97.03.10 97WO-EP01203</p>	<p>C(7-D12, 14-U1A, 14-V1, 14-V2, 14-V3) .3</p> <div data-bbox="873 184 1291 388"> </div> <p style="text-align: right;">(I)</p> <p style="text-align: right;">reactant (ix)</p> <p>X = O or S; R₁ = 1-4C haloalkyl; R₂ = H or halogen; R₃ = H, CN, CNS, halogen, 1-4C haloalkyl, 1-4C haloalkoxy or 1-4C haloalkylthio; R₄ = H, CN, CNS, halogen, 1-4C alkyl, 1-4C haloalkyl, 1-4C alkoxy, 1-4C haloalkoxy, 1-4C haloalkylthio or alkylaminocarbonyl; R₅ = (i) H, CN, NO₂, OH, NH₂, halogen, 1-4C alkylamino (optionally</p>
<p>Substituted 1-methyl-3-benzyl-6-haloalkyl-uracil derivatives of formula (I) and their salts and enol ether derivatives are new.</p>	<p>WO 9735845-A+</p>

<p>substituted by 1-4C alkyl, (1-4C)alkylcarboxyl (sic) or (1-4C)alkoxycarbonyl, haloalkoxy or haloalkylthio; or (ii) alkoxy, alkylthio, cycloalkoxy, cycloalkylthio, alkenyloxy, alkenylthio, alkyniloxy, alkynylthio, alkylcarboxyloxy, alkylcarbonylthio, alkenylcarbonyloxy, alkenylcarbonylthio, alkylsulphonyloxy, alkylsulphonylthio, alkylsulphonyloxy (all optionally substituted by 1-3 of (a) halogen, NO₂, CN, OH, cycloalkyl, alkoxy, cycloalkoxy, alkenyloxy, alkyniloxy, alkoxyalkoxy, alkylthio, alkylsulphonyl, alkylsulphonyl and 1-6C alkylideneamino; (b) phenyl, phenoxy or phenylsulphonyl (all optionally substituted by 1-3 of halogen, NO₂, CN, alkyl, alkoxy and haloalkyl); (c) 3-7 membered heterocyclyl or heterocyclyloxy (both optionally substituted by 1-3 of halogen, NO₂, CN, alkyl, alkoxy, haloalkyl and alkylcarbonyl); and (d) COR₇, COOR₇, COSR₇, CONR₇R₈, OCOR₇, OCOOR₇, OCOSR₇, OCONR₇R₈ or NR₇R₈; R₇ = H, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkylalkyl, alkenyloxyalkylalkyl, phenyl or phenylalkyl (where phenyl moieties are optionally substituted by 1-3 of halogen, NO₂, CN, alkyl, haloalkyl, alkoxy and alkylcarbonyl);</p>	<p>R₈ = H, OH, alkyl, cycloalkyl, alkoxy, alkoxyalkylalkoxy, alkenyl or alkenyloxy; or NR₇R₈ = 3-7 membered heterocycle (optionally substituted by 1-3 of halogen, NO₂, CN, alkyl, haloalkyl, alkoxy and alkylcarbonyl); R₆ = (1) OH, SH, haloalkoxy or haloalkylthio; (2) alkoxy, alkylthio, cycloalkoxy, cycloalkylthio, alkenyloxy, 5-7C cycloalkenyloxy, alkenylthio, alkyniloxy, alkynylthio, alkylcarbonyloxy, alkylcarbonylthio, alkoxyalkoxy, alkenylcarbonyloxy, alkenylcarbonylthio, alkylsulphonyloxy, alkylsulphonylthio, alkylsulphonyloxy [all optionally substituted by 1-4 groups selected from groups (a)-(d) given in R₅ (ii) (except that the Ph, PhO and PhSO₂ in (b) may additionally be substituted by alkoxyalkoxy), =O, =N-OR₂₀, -C(R₂₁)=N-OR₂₀ and SiR₃₀R₃₁R₃₂]; or (3) -CYR₁₁, -CR₁₁(Z₁R₁₂)(Z₂R₁₃), -C(R₁₁)=C(R₁₄)-Q, -CHR₁₁CHR₁₄COR₁₅, COOR₁₉, -C≡CCONHOR₂₀, -C≡CCON(R₁₉)OR₂₀, -C≡CCSNHOR₂₀, -C≡CCSN(R₁₉)OR₂₀, -C≡CC(R₂₁)=NOR₂₀, -NR₂₃R₂₄ or -C≡C-Q'; R₃₀-R₃₂ = alkyl or 2-6C alkenyl; Z₁, Z₂ = O or S; Q = CN, COR₁₅, CH₂COR₁₅, -C(R₁₆)=C(R₁₇)COR₁₅,</p> <p style="text-align: right;">WO 9735845-A+/1</p>
--	--

<p>97-526074/48</p> <p>CH₂CHR₁₈COR₁₅, CONHOR₂₀, CON(R₁₉)OR₂₀, CSNHOR₂₀, CSN(R₁₉)OR₂₀, C(R₂₁)=NOR₂₀ or Q'; Q' = heterocycle of formula (a);</p> <div data-bbox="321 1564 516 1669"> </div> <p>(a)</p> <p>Q'' = O or S; Alk = 1-3C alkylene (optionally substituted by alkyl); R₁₁ = H, CN, alkyl, haloalkyl, 2-6C alkenyl, 2-6C alkynyl, cycloalkyl, alkoxyalkyl or alkoxyalkoxy; R₁₂, R₁₃ = alkyl, haloalkyl, alkenyl, alkynyl or alkoxyalkyl; or R₁₂+R₁₃ = 2-4 membered hydrocarbon chain which (i) is saturated or unsaturated, (ii) is optionally substituted by =O, (iii) optionally has one member (not adjacent to Z₁ or Z₂) replaced by O, S or N, (iv) is optionally substituted by 1-3 of CN, NO₂, NH₂, halogen, alkyl, 2-6C alkenyl, alkoxy, 2-6C alkenyloxy, 2-6C alkynyloxy, haloalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl,</p>	<p>alkenyloxyalkyl, alkynyloxyalkyl, cycloalkyl, cycloalkoxy, COOH, alkoxyalkoxy, alkylcarbonyloxyalkyl and phenyl (itself optionally substituted by 1-3 of CN, NO₂, NH₂, halogen, alkyl, haloalkyl, alkoxy and alkoxyalkoxy) and (v) optionally has 1 or 2 members forming part of a 3-7 membered ring (optionally containing 1 or 2 of O, S, N and N(alkyl) as heteroatom(s) and optionally substituted by 1 or 2 of CN, alkyl, 2-6C alkenyl, alkoxy, cyanoalkyl, haloalkyl and alkoxyalkoxy); R₁₄ = H, CN, halogen, alkyl, haloalkyl, alkoxy, alkylcarbonyl or alkoxyalkoxy; R₁₅ = H, OR₂₂, SR₂₂, alkyl (optionally mono- or disubstituted by alkoxy), 2-6C alkenyl, 2-6C alkynyl, haloalkyl, cycloalkyl, alkylthioalkyl, alkyliminooxy, NR₂₃R₂₄ or phenyl (optionally substituted by 1-3 of CN, NO₂, halogen, alkyl, 2-6C alkenyl, haloalkyl, alkoxy and alkoxyalkoxy); R₂₂ = as R₁₉; R₂₃, R₂₄ = H, alkyl, 2-6C alkenyl, 2-6C alkynyl, cycloalkyl, haloalkyl, alkoxyalkyl, alkylcarbonyl, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyalkoxy (2-6C)alkenyl (optionally substituted in the</p> <p style="text-align: right;">WO 9735845-A+/2</p>
---	---

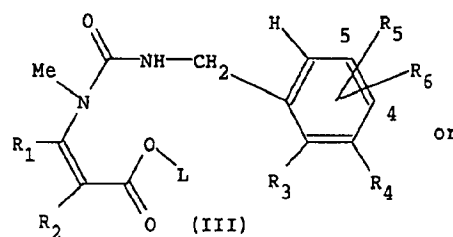
(con't)

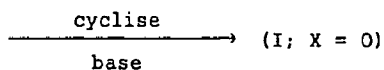
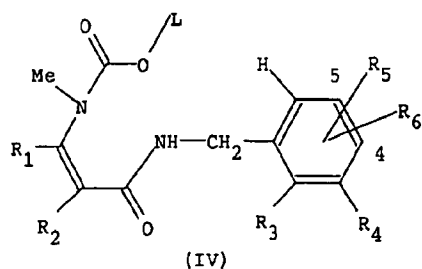
R₁₉ = (i) H; (ii) alkyl, haloalkyl, 2-6C alkenyl or 2-6C alkynyl (all optionally substituted by 1 or 2 of CN, halogen, OH, COOH, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkenyloxy, carbonyl and -CO-Het); (iii) alkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, mono- or dialkylaminocarbonyl, alkoxyiminoalkyl or cycloalkyl; or (iii) phenyl or phenylalkyl (both optionally ring-substituted by 1-3 of CN, NO₂, halogen, alkyl, haloalkyl, alkoxy and alkoxycarbonyl):

R₂₁ = (i) H or halogen; (ii) alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyloxy, alkylthio, haloalkylthio, alkylcarbonyloxy, haloalkylcarbonyloxy, alkylsulphonyloxy or haloalkylsulphonyloxy (all optionally monosubstituted by OH, CN, COOH, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, mono- or dialkylaminocarbonyl, or alkylcarbonyloxy); (iii) -CO-Het; (iv) alkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkoxycarbonyloxy, alkylcarbonylthio, haloalkylcarbonylthio, alkoxycarbonylthio, 2-6C alkenyl, 2-6C alkenylthio, alkynyl, alkynyloxy, alkynylthio, (2-6C) alkynylcarbonyloxy, alkynylsulphonyloxy, cycloalkyl, cycloalkoxy, cycloalkylthio, cycloalkylcarbonyloxy or cycloalkylsulphonyloxy; or (v) phenyl, phenoxy, phenylthio, benzoyloxy, phenylsulphonyloxy.

R₂₇ = (i) H, OH, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, alkoxyalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, 5-7C cycloalkenyloxy, haloalkoxy, haloalkenyloxy, hydroxyalkoxy, cyanoalkoxy, cycloalkyloxy, alkoxyalkoxy, alkoxyalkenyloxy, alkylcarbonyloxy, haloalkylcarbonyloxy, alkylcarbamoyloxy, haloalkylcarbamoyloxy, alkylcarbonylalkyl, alkoxy carbonylalkyl, alkylcarbonylalkoxy, alkoxy carbonylalkoxy, alkylthioalkoxy or dialkylaminoalkoxy; (ii) phenyl, phenylalkoxy, phenylalkenyloxy or phenylalkynyloxy (all optionally ring-substituted by 1-3 of CN, NO₂, halogen, alkyl, haloalkyl, 2-6 alkenyl, alkoxy and alkoxy carbonyl; and with 1 or 2 CH₂ units of the aliphatic chains optionally replaced by O, S or N(alkyl)); (iii) heterocyclyl, heterocyclylalkoxy, heterocyclylalkenyloxy or heterocyclylalkynyloxy (all optionally ring-substituted by 1-3 of CN, NO₂, halogen, alkyl, haloalkyl, 2-6 alkenyl, alkoxy and

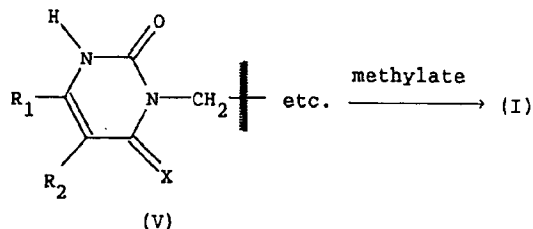
unless specified otherwise alkyl moieties have 1-6C and alkenyl, alkynyl and cycloalkyl moieties have 3-6C.





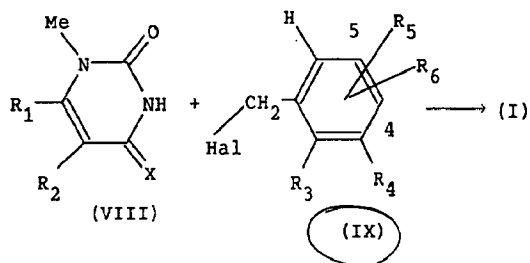
L = alkyl or phenyl.

(b)



WO 9735845-A/6

(c)

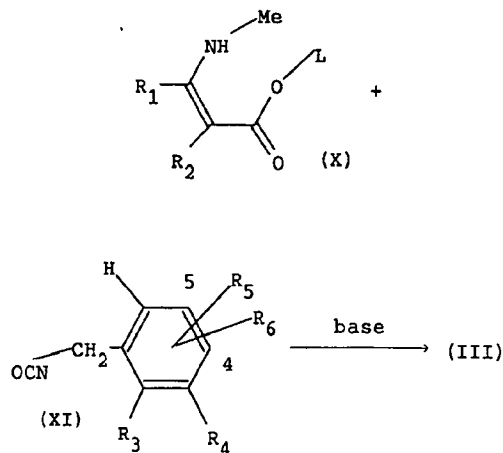


Reaction is in presence of base, or (VIII) is used in alkali metal salt form.

STARTING MATERIALS

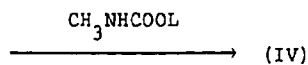
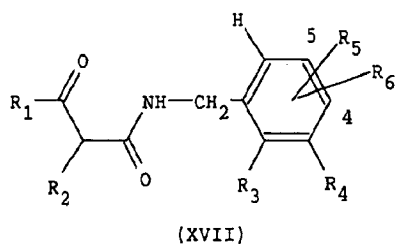
(III) and (IV) are prepared e.g. as follows.

(a)



WO 9735845-A/7

(b)



EXAMPLE

A solution of 1.8g 3-(2,3-dichloro-4-isopropoxybenzyl)-2,4-dioxo-1H-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine in 50 ml DMF was treated with 0.7g K_2CO_3 and 0.7g MeI, stirred for 18 hrs. and treated with 150 ml ice-water. The solid product was isolated to give 1.4g of 3-(2,3-dichloro-4-isopropoxybenzyl)-2,4-dioxo-1-methyl-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine (Ia), m.pt. 167-168°C.

BIOLOGICAL ACTIVITY

(Ia) at 3.9 and 7.8 g/ha post-emergence showed good selective herbicidal activity against *Abutilon theophrasti*, *Amaranthus retroflexus* and *Solanum nigrum* in wheat. (RMH)

(117pp2400DwgNo.0/0)

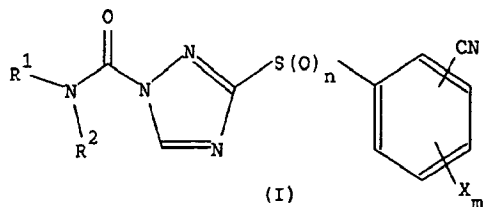
SR:WO9504461

WO 9735845-A/8

95-187191/25 C02 FARB 93.11.23
 BAYER AG *EP 654468-A1
 93.11.23 93DE-4339863 (95.05.24) C07D 249/12, A01N 47/38
 Substd. carbamoyl-triazole derivs. - useful as herbicides esp.
 selective herbicides for weed control in crops (Ger)
 C95-086934 R(BE CH DE ES FR GB IT LI NL)
 Addnl. Data: ANDREE R, DOLLINGER M, SANTEL H
 94.11.10 94EP-117746

C(7-D13, 14-U1A, 14-V2) .3

Substd. carbamoyl triazole derivs. of formula (I) are new:



m = 0-4;
 n = 0-2;
 R¹, R² = opt. substd. alkyl, alkenyl or alkynyl; or

R¹+R² = alkanediyl;
 X = halogen, OH, NH₂, SH or opt. substd. alkyl, alkoxy, alkylthio, alkylamino, alkanoylamino, alkylsulphonylamino, cycloalkoxy, cycloalkylthio, cycloalkylamino, cycloalkylalkoxy, cycloalkylalkylthio, cycloalkylalkylamino, aryloxy, arylthio, arylamino, arylcarbonyl, arylsulphonyl, arylalkyl, arylalkoxy, arylalkylthio, arylalkylamino, arylalkylcarbonyl or arylalkylsulphonyl.

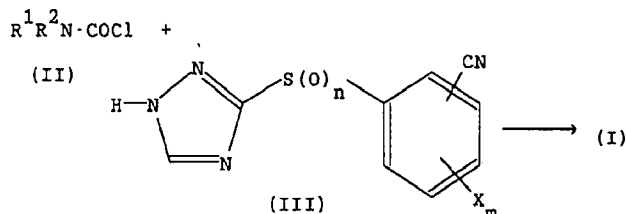
Also claimed are substd. triazoles of formula (III) (see "Preparation").

USE

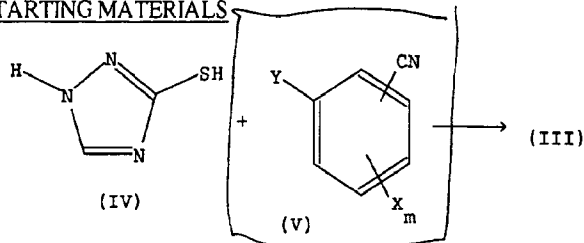
(I) are defoliants, desiccants and esp. herbicides. They are esp. suitable for the selective control of weeds in crops such as cereals, beet, soya and cotton. (III) are intermediates in the prepn. of (I).
 Suitable amts. for use are 10 g-10 kg/ha., esp. 50 g -5 kg/ha..

EP 654468-A+

PREPARATION



STARTING MATERIALS



Y = halogen.

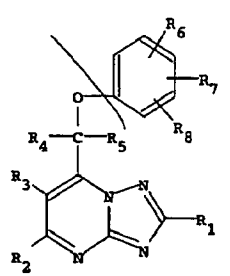
EXAMPLE

A mixt. of 3.5 g 3-(4-cyano-2,5-difluorophenylthio)-1H-1,2,4-triazole, 2.1 g N,N-diethylcarbonyl acid chloride and 20 ml pyridine were stirred for 3 days at 20 °C. The mixt. was then diluted to double vol. with water, filtered and washed with 1N HCl and water. 5.5 g (91.5% yield) 3-(4-cyano-2,5-difluorophenylthio)-1-diethylaminocarbonyl-1H-1,2,4-triazole of m.pt. 80 °C were thus obtd.

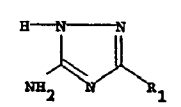
This cpd. had 80%, 90%, and 50% effectiveness against *Galium*, *Ipomoea* and *Alpecurus* resp., without harming rape or cotton plants. (AC)

(16pp1401DwgNo.0/0)
 SR:EP332133 EP422369

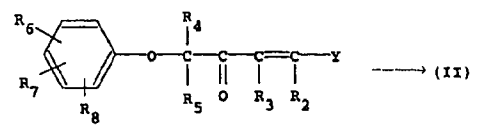
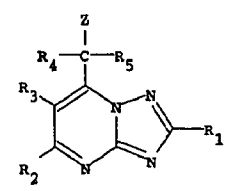
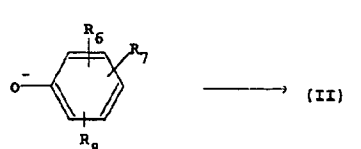
EP 654468-A

<p>95-161726/21 B02 BOOT 93.10.13 BOOTS CO PLC *WO 9510521-A I 93.10.13 93GB-021162 (95.04.20) C07D 487/04, A61K 31/505 (C07D 239:00, 249:00, 487/04) New and use of 1,2,4-triazolo[1,5-a]pyrimidine cpds. - for treatment and/or prevention of seizures, epilepsy and neurological damage e.g. stroke, brain trauma, head injury or haemorrhage (Eng) C95-074901 N(AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN) R(AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ) Addnl. Data: HEAL D J, FERNANDEZ FERNANDEZ M I, SARGENT B 94.10.12 94WO-EP03364</p>	<p>B(6-D9, 14-J7, 14-N16) .3</p> <div style="text-align: center;">  <p>(II)</p> </div> <p>R₄, R₅ = H, 1-6C alkyl, opt. substd. by one or more of halo, CN, OH, NH₂ or 1-6C alkyl; or</p> <p style="text-align: right;">WO 9510521-A+</p>
<p>1,2,4-triazolo[1,5-a]pyrimidine cpds. of formula (II) and their salts are new:</p> <p>R₁ = H or 1-6C alkyl, 1-6C alkoxy or 1-6C alkanoyl opt. substd. by one or more of halo, CN, OH or NH₂; R₂, R₃ = H or 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkylthio, 1-6C alkylsulphonyl or 1-6C alkylsulphonyl opt. substd. by one or more of halo, CN, OH or NH₂;</p>	

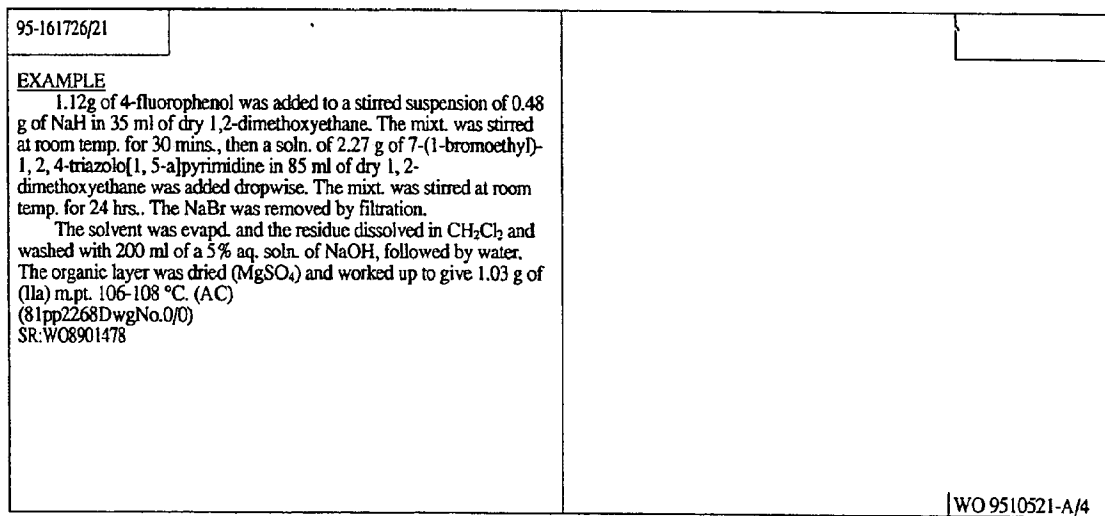
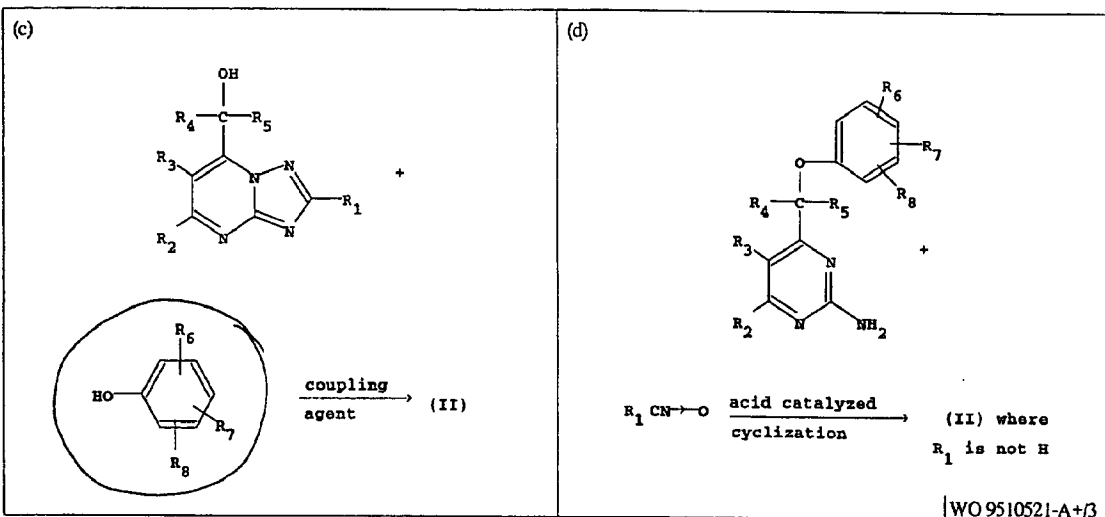
(c) 1995 Derwent Information Ltd

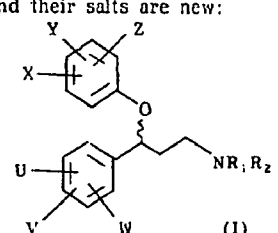
<p>CR₄R₅ = 3-6C cycloalkylidene opt. substd. by one or more of halo, CN, OH, NH₂ or 1-6C alkyl; R₆, R₇, R₈ = H, halo, OH, SH, CN or 1-6C alkyl, 1-6C alkanoyl, 1-6C alkoxy, 2-6C alkoxycarbonyl, carboxy, 1-6C alkanoyloxy, 1-6C alkylthio, 1-6C alkylsulphonyl, 1-6C alkylsulphonyl, 1-6C alkylsulphonylamino, sulphanoyl, carbamoyl, 2-6C alkylcarbamoyl or 1-6C alkanoylamino opt. substd. by one or more of halo, CN, OH or amino and any N atom is opt. substd. by one or more 1-6C alkyl; with the proviso that if R₁, R₂, R₃, R₄ and R₈ = H; R₅ = Me and either R₆, R₇ = H or R₈ = 4-chloro and R₇ is H or 2-chloro then cpd. (II) is not a racemate.</p> <p>Also claimed is the use of cpds. (I), which are cpds. (II) excluding the proviso, as pharmaceuticals.</p> <p>USE Cpds. (I) and (II) can be used for the treatment, prophylaxis and/or inhibition of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage, e.g. stroke, brain tumour, head injuries and haemorrhage. Cpds. (I) and (II) potentiate GABA-A transmission and/or activate neuronal K⁺ channels.</p>	<p>Admin. may be oral, rectal, parenteral or topical. Typical unit dosage is 1-1,000 mg. pref. 5-500 mg.</p> <p>SPECIFIC COMPOUNDS 21 cpds. (I) are claimed, e.g.: 7-[1-(4-fluorophenoxy)ethyl]-1,2,4-triazolo[1,5-a]pyrimidine (IIa); 7-[1-(4-methylsulphonylphenoxy)ethoxy]-1,2,4-triazolo[1,5-a]pyrimidine; 7-[1-(2-chloro-4-fluorophenoxy)ethyl]-1,2,4-triazolo[1,5-a]pyrimidine.</p> <p>PREPARATION Cpds. (II) are prepd. as follows (claimed): (a)</p> <div style="text-align: center;">  </div> <p style="text-align: right;">WO 9510521-A+/1</p>
--	--

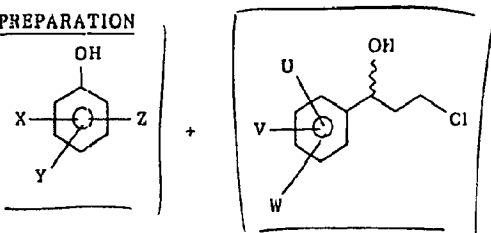
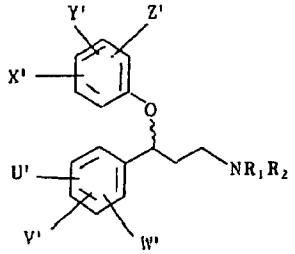
(c) 1995 Derwent Information Ltd

<p>95-161726/21</p> <div style="text-align: center;">  <p>(II)</p> </div> <p>Y = a leaving gp.</p> <p>(b)</p> <div style="text-align: center;">  </div>	<div style="text-align: center;">  <p>(II)</p> </div> <p>Z = a leaving gp.</p> <p style="text-align: right;">WO 9510521-A+/2</p>
---	--

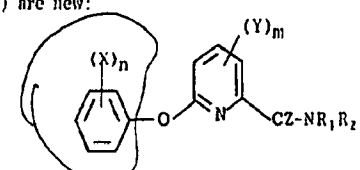
(con't)

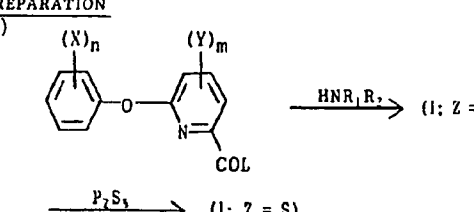
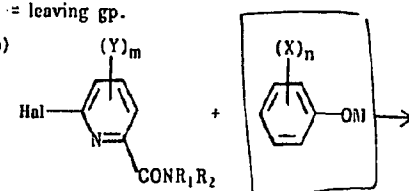


<p>92-398487/48 BOS UYPE- 91.05.01 UNIV PENNSYLVANIA *WO 9219210-A2 91.05.01 91US-694346 (92.11.12) A61K Novel serotonin re-uptake inhibitor cpds. - are antidepressants, also useful for imaging serotonin receptors when contg. radioactive halogen isotopes (Eng) C92-176712 N(CA JP) R(AT BE CH DE DK ES FR GB GR IT LU MC NL SE; Addnl. Data: KUNG H F 92.04.22 92WO-US03261</p>	<p>B(5-A3A, 5-A3B, 5-B1B, 7-H, 10-A4, 10-A8, 10-A10, 10-A13D, 10-A15, 10-A18, 10-A19, 10-B1A, 10-B2B, 11-C7B5, 12-C10, 12-G1, 12-K4A5) U, V, W, X, Y, Z = H, halo or 1-4C alkyl or 1-4C alkoxy (both opt. substd. by halo and/or OH), 1-6C hetero- cycle, 1-4C thioalkyl, NR₃R₄, -R₅-A-R₆, -A-R₇, CN, SO₂R₈, NHCONH₂ or CONR₃R₄; R₁-R₄ = H or 1-4C alkyl; R₅, R₆ = 1-6C alkyl; R₇ = H, 1-6C alkyl, 1-6C heterocycle or -A-R₅; R₈ = 1-4C alkyl or NR₃R₄; A = S, NH or O; provided that at least one of U-Z = halo.</p>
<p>Substd. 3-phenoxy-3-phenylpropylamine derivs. of formula (I) and their salts are new:</p>  <p>(I)</p>	<p>Intermediate cpds. of formula (II) (see "Preparation") are also new.</p> <p>USE</p> <p>(I) bind to neurotransmitter reuptake sites and esp. inhibit serotonin reuptake. Radioactive halogen (esp. ¹²⁵I) labelled cpds. of (I) are useful for imaging serotonin receptors using single photon emission tomography (SPECT) to assess and improve treatment of psychiatric disorders. (I) may also be useful for in vitro binding studies and as therapeutic agents.</p> <p>WO9219210-A+</p>

<p>SPECIFICALLY CLAIMED N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propyl- amine (Ia).</p> <p>PREPARATION</p>  <p>HNR₁R₂ → (I)</p> <p>Radioactive I-labelled cpds. of (I) are prepd. by treating the corresp. Br-cpd. with Et₃N/tetrakis(triphenyl)- phosphine palladium, then stirring the resulting tributyltin deriv. (IIa) with I₂/CHCl₃ or NaI/H₂O₂(aq.).</p> <p>Other intermediates within the scope of (II) may be used to prepare the radiolabelled cpds. in an analogous manner.</p>	 <p>(II)</p> <p>one of U', V', W', X', Y', Z' = Sn(R)₃, Si(R)₃, or HgR and the others are as defined for U-Z; R = 1-5C alkyl.</p> <p>EXAMPLE</p> <p>A mixt. of (R)-(+)-1-chloro-3-phenyl-3-(4-iodo-2-methylphenoxy)propane (0.58 g), eq. MeNH₂ (40%, 4 ml)</p> <p>WO9219210-A+/1</p>
---	---

<p>92-398487/48</p> <p>and EtOH (1.5 ml) was heated at 130°C for 3 hr. in a sealed tube and worked up to give 0.25 g (44%) (R)-(-)-(Ia) α_D²⁵ = +11.98 (c 3.32, CHCl₃); HCl salt had m.pt. 68°C, α_D²⁵ = -8.34 (c 0.82, CHCl₃).</p> <p>In in vitro competitive binding assays using rat brain tissue prepn. (Ia). HCl had K_i 5 nM (serotonin uptake, (³H-paroxetine)) and IC₅₀ 20 nM (norepinephrine uptake, (³H-nisoxetine)). (26pp2218AFDwgNo0/3).</p> <p>SR:No-SR.Pub</p>	<p>WO9219210-A/2</p>
--	----------------------

<p>92-185374/23 C02 SHELL INT RES MIJ BV 90.11.28 90GB-025828 (92.06.03) C07D 213/86, A01N 43/40, C07D 213/78, 213/81, 213/83 New 2-phenoxy-pyridine-6-(thio)carboxamide derivs. - useful as herbicides, against grasses and broadleaf weeds with selectivity to small grain cereals (Eng) C92-084848 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE) Addnl. Data: FOSTER C J, GILKERSON T, STOCKER R, GILMORE I J 91.11.26 91EP-203092</p>	<p>SHEL 90.11.28 *EP 488474-A1 C(7-D4, 12-P6)</p>
<p>2-Phenoxy-6-pyridine-(thio)carboxamide derivs. of formula (1) are new:</p>  <p>(1)</p> <p>n = 1-5; X = H; halo; alkyl or alkoxy (opt. substd. by halo, CN, OH and/or alkoxy), CN, NO₂, alkenyloxy, alkynyloxy, alkylthio, haloalkylthio, alkenylthio or alkynylthio; m = 0-3; Y = halo, alkyl or haloalkyl;</p>	<p>Z = O or S; R₁, R₂ = H, alkyl opt. substd. by 1 or more of halo, OH, CN, alkoxy, alkylthio, alkoxy-carbonyl or mono- or di-alkylamino, alkenyl, alkynyl, cycloalkyl, or opt. substd. cycloalkylalkyl, or OH, alkoxy, alkenyloxy, alkynyloxy, alkoxy-carbonyl, NH₂, mono- or di-alkylamino, alkoxy-carbonylamino, arylamino opt. substd. by a halo, or dialkylcarbamoyl; or R₁ + R₂ = alkylene opt. interrupted by O, S or NR; and R = H or alkyl.</p> <p>MORE SPECIFICALLY n = 1-2 (esp. 1); X = H, F, Cl, Br, NO₂, Et, OMe or CF₃ (esp. 3-CF₃, 3-OMe or 3-Cl); R₁ = H, 1-4C alkyl or 2-4C alkenyl (esp. H); R₂ = H, 1-8C alkyl, 1-4C alkyl substd. by F, OH, CN, OMe, OEt, COOMe, COOEt or mono- or di-(1-2C alkyl)-amino, 3-6C cycloalkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C alkoxy, 1-4C alkylamino, 2-4C alkenyloxy, COOMe, COOEt, 3-7C alkoxy-carbonylamino, di(1-2C</p> <p>EP-488474-A+</p>

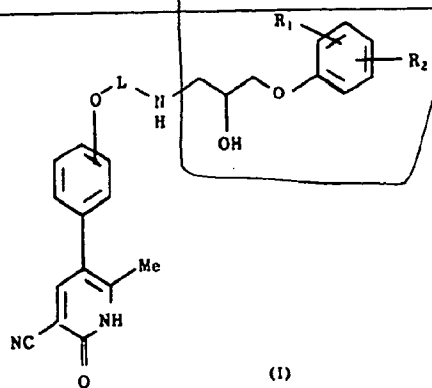
<p>alkyl)carbamoyl, arylamino (opt. substd. by halo) or halo-(3-6C)cycloalkyl-(1-4C)alkyl (esp. Et, Pr, cyclopropyl or cyclobutyl); or R₁ + R₂ = (CH₂)₄, (CH₂)₂O(CH₂)₂ or (CH₂)₂NR(CH₂)₂; R = Me or Et.</p> <p>USE/ADVANTAGE (1) are herbicides active against a wide spectrum of grasses and esp. broadleaved weeds (e.g. blackgrass, wild oat, giant foxtail, green foxtail, morning glory, cleavers, black nightshade, speedwell and chickweed), when applied pre- or post-emergence. They exhibit selectivity to small grain cereals (e.g. maize, wheat, barley and rice) and to broad-leaf crops (e.g. soya, sunflower and cotton). Application rate is 0.01-10 (pref. 0.03-4) kg/ha.</p> <p>PREPARATION (n)</p>  <p>(1; Z = S)</p>	<p>L = leaving gp. (b)</p>  <p>(1; Z = O)</p> <p>M = alkali metal.</p> <p>EXAMPLE A mixt. of 6-(3-trifluoromethylphenoxy)picolinic acid (1.5g) and SOCl₂ (20 ml) was refluxed for 1 hr. Excess SOCl₂ was evapd. in vacuo and CH₂Cl₂ (20 ml) added. A soln. of n-propylamine (0.6g) and Et₃N (1g) in CH₂Cl₂ (20 ml) was added dropwise at ambient temp. After work-up, the residue was purified by silica gel chromatography, eluting with 5% (v/v) ether/CH₂Cl₂, to give 1.5g. N-n-propyl-2-(3-trifluoromethylphenoxy)-6-pyridinecarboxamide (1a) as an oil. (1a) was applied (pre-emergence) at (a) 5 and (b) 1 kg/ha. 12 Days after applicn. herbicidal effect (0 = no effect; 9 = complete kill) was assessed visually.</p> <p>EP-488474-A+1</p>
---	---

<p>92-185374/23</p> <p>Results were: (a): barnyard grass (BG), oats (O), mustard (M), sugar-beet (SB) 9; maize (Mz), rice (R), linseed (L) 8; soya-bean (S) 7. (b): BG, M, SB 9; O 8; S 7; Mz, R, L 6. (38pp985PHPDwgNo0/0). SR: 1. Jnl. Ref EP176 EP53011 JP63017811 US4251263 US4270946</p>	<p>EP-488474-A/2</p>
---	----------------------

91-088869/13 B03 GLAX 22.09.89
GLAXO INC *EP -419-286-A
09.08.90-US-565297 (+US-411065) (27.03.91) A61k-31/43
C07d-213/85
New phenoxy-substd. pyridone nitrile(s) - are used in treating
cardiovascular disease, esp. congestive heart failure
C91-037751 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

Pyridone derive. of formula (I) and their acid addn. salts
are new:

B(7-D4C, 12-F1C)



R₁, R₂ = H, lower alkoxy, morpholino, CN, halo, CF₃,
EP-419286-A+

alkyl (opt. substd. by alkoxy or cycloalkylalkoxy),
alkylsulphonyl, NO₂, OH, alkenyloxy, NH₂ or mono-
or di-alkylamino;
L = (CR₄R₄)_n CON(R₄)CR₇CR₈R₉ (gp. (a)) or
(CR₁₀R₁₁)_p;
R₁ - R₁₁ = independently H or lower alkyl;
n = 1-3;
p = 2-6.

MORE SPECIFICALLY

L = (a; n = 1-3) or (b; p = 3) and OL is at the 4-position,
R₁-R₇, R₁₀ and R₁₁ = H;
R₈ and R₉ = H or Me;
either
(1) R₁ = H;
R₂ = CN, Cl or Me;
(2) R₁ = H;
R₂ = H, CN or Cl; or
(3) R₁ = H or Cl;
R₂ = H, CN or Cl at the 2-position.

USE

(I) are positive inotropic and β-adrenergic agents useful
for treating congestive heart failure. Dose is 0.1-5 μg/kg 1-4
times a day.

SPECIFICALLY CLAIMED

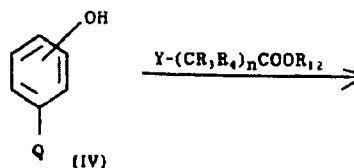
13 Cpd. (I) e.g. 5-(4-(N-(2-(3-phenoxy-2-hydroxy-
propylamino)ethyl)carbamoylmethoxy)phenyl)-6-methyl-2-
oxo-1,2-dihydro-3-pyridinecarbonitrile (Ia);
5-(4-(N-(2-(3-(2-cyanophenoxy)-2S-hydroxypropylamino)-
2-methylpropyl)carbamoylpropoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile; and
5-(4-(N-(2-(3-(2-chlorophenoxy)-2S-hydroxypropylamino)-
2-methylpropyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile.

WIDER DISCLOSURE

Intermediates of formula (VI), (VII), (X), (XVII) and
(XVIII) are stated to form part of the invention.

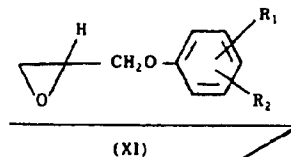
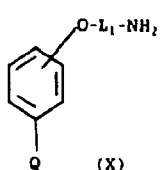
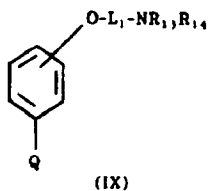
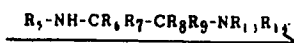
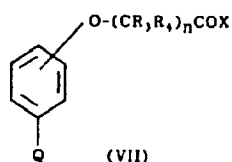
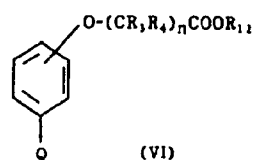
PREPARATION

(I)



EP-419286-A+/1

91-088869/13



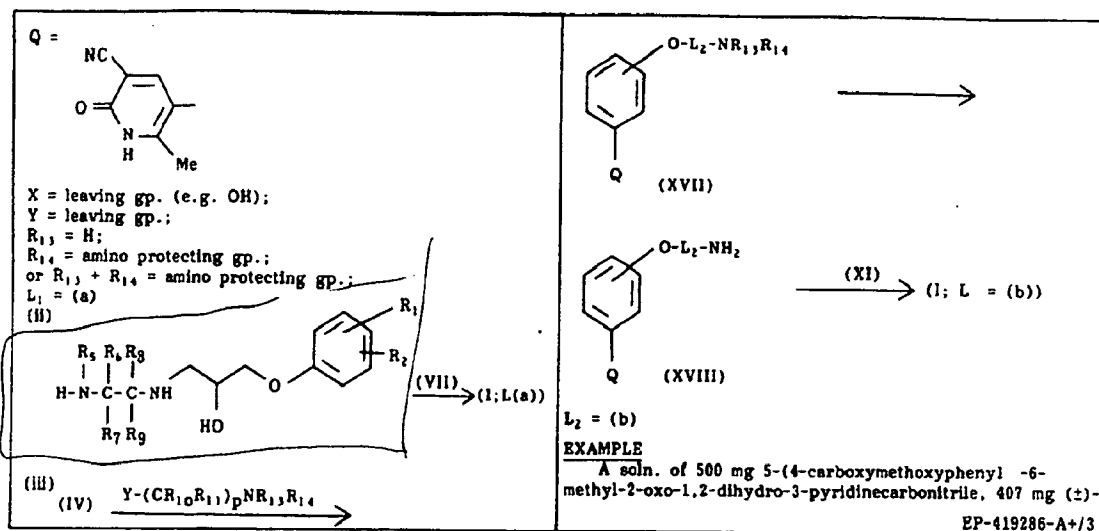
(I; L=(a))

EP-419286-A+/2

BEST AVAILABLE COPY

(con't)

(C) 2004 Copyright Derwent Information Ltd.

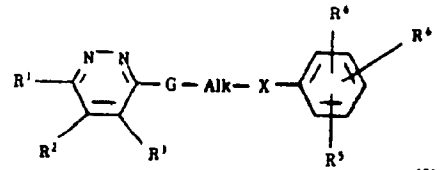
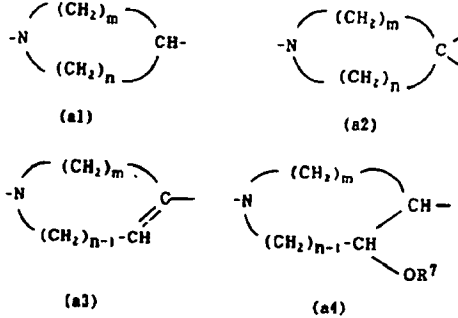


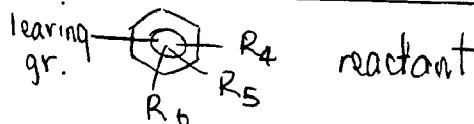
91-088869/13

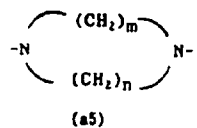
-N-(2-aminoethyl)-2-hydroxy-3-phenoxypropylamine and 316 mg diethyl cyanophosphonate in 10 ml DMF is cooled (ice bath) and treated dropwise with 540 μ l Et₃N in 2 ml DMF. The mixt. is allowed to slowly warm to room temp., stirred overnight under N₂ then evapd. in vacuo. The residue is chromatographed over silica gel, eluting with CHCl₃/MeOH/NH₄OH (90:10:2). The solid is recrystd. from EtOAc/MeOH to give 185 mg (21%) (1a), m.pt. 136-138°C. (29pp985HBDwgNo0/0)

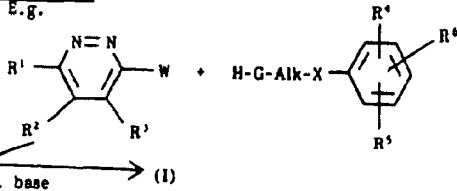
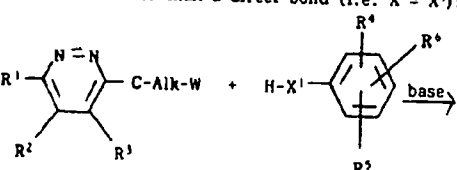
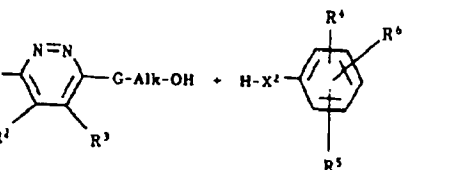
(E) ISR: No Search Report.

EP-419286-A/4

<p>91-065362/09 803 JANSEN PHARMACEUT NV 09.11.88-US-269805 (+US-124530) (12.02.91) A61k-31/50 C07d-237/34 C07d-401/04 C07d-403/04 New antiviral pyridazine-amine derivs. - esp. useful against disease caused by picornaviruses C91-027693</p>	<p>JANU 23.11.87 *US 4992-433-A B(6-D6, 7-D10, 12-A6, 12-A7, 12-D7, 12-E1, 12-F18, 12-J1, 12-K2, 12-K6, 12-L4)</p>
<p>Pyridazinamine derivs. of formula (I) and their acid addn. salts and stereoisomers are new:</p>  <p>(I)</p> <p>R¹ = H, 1-6C alkyl, halo, OH, SH, CF₃, NH₂, mono- or di(1-6C alkyl)amino, CN, 1-6C alkoxy, aryloxy, aryl (1-6C)alkoxy, 1-6C alkylthio, arylthio, 1-6C alkylsulphiny, 1-6C alkylsulphonyl, arylsulphiny, arylsulphonyl, 1-6C alkoxycarbonyl, 1-6C alkylcarbonyl</p>	<p>or aryl; R², R³ = H or 1-6C alkyl; or R₂ + R₃ is -CH=CH-CH=CH-; G = divalent cyclic amine moiety of formulae (a1)-(a5):</p>  <p>(a1) (a2) (a3) (a4)</p> <p>US4992433-A+</p>



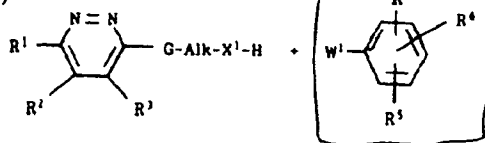
 <p>(a5)</p> <p>In (a1) - (a5) 1 or more C atoms are opt. substd. by 1-6C alkyl, or 2C atoms may be bridged by a 2-4C alkylene gp.; m, n = 1-4; (m + n) = 3, 4 or 5; R⁷ = H, 1-6C alkyl or aryl (1-6C)alkyl; Alk = 1-6C alkylene; X = O, S or NR⁸; R⁸ = H or 1-6C alkyl; R⁴, R⁵, R⁶ = H, 1-6C alkyl, 1-6C hydroxyalkyl, halo, NH₂, CN, NO₂, 1-6C alkoxy, OH, 1-6C alkylthio, SH or CF₃; and R⁴ may also be 4,5-dihydro-2-oxazolyl or 2-oxazolyl, both opt. substd. with 1 or more 1-6C alkyl or hydroxyalkyl gps. 5,6-dihydro-4H-1,3-oxazin-2-yl or 4H-1,3-oxazin-2-yl, both opt. substd. with 1 or more 1-6C alkyl, or hydroxyalkyl gps.; aryl; or a gp. of formula -Z¹-C(=Y)-Z²-R¹²; Z¹ = O, S, NR⁹, CH₂ or a direct bond;</p>	<p>Z² = O, S, NR¹⁰ or a direct bond; Y = O, S or NR¹¹; R⁹⁻¹¹ = H or 1-6C alkyl; R¹² = H, 1-6C alkyl, aryl, 3-6C cycloalkyl, aryl (1-6C)alkyl, 3-6C cycloalkyl (1-6C)alkyl, 3-6C alkenyl, 3-6C alkynyl, 1-6C hydroxyalkyl, 1-6C alkoxy (1-6C)alkyl, amino (1-6C)alkyl, or mono- or di(1-6C alkyl)amino (1-6C)alkyl; or R¹² may also be halo or hydrazino when Z¹ = bond or CH₂, Y = O and Z² = bond; aryl = phenyl, opt. substd. by 1-3 of halo, 1-6C alkyl, CF₃, NO₂, NH₂, 1-6C alkoxy, OH or 1-6C alkoxy-carbonyl. Anti-picornaviral compns. and methods using (I) as active agent are also claimed.</p> <p>USE/ADVANTAGE (I) have potent local and systemic antiviral activity at very low doses and have low cytotoxicity. Activity is shown against a broad spectrum of picornaviruses, including poliovirus type 1, 2 and 3; coxsackieviruses echovirus, enteroviruses, e.g. enterovirus 70 and esp. rhinoviruses, e.g. Human rhinovirus serotypes HRV-2, -3, -4, -5, -6, -9, -14, -15, -29, -39, -41, -51, -59, -63, -70, -72, -85, -86, -89, etc.</p> <p>US4992433-A+/1</p>
---	--

<p>91-065362/09</p> <p>(I) can be used in treatment and prevention of e.g. common cold, pneumonia, bronchiolitis, herpangina, paralysis, aseptic meningitis, encephalitis, pericarditis, myocarditis, hepatitis, gastrointestinal diseases, acute haemorrhagic conjunctivitis, and dermatological diseases e.g. exanthema, hand-foot-and-mouth disease, etc. Doses are e.g. 0.001-50. pref. 0.01-10 mg/kg.</p> <p>SPECIFICALLY CLAIMED Ethyl 4-(2-(1-(6-methyl-3-pyridazinyl)-4-piperidinyl)ethoxy)benzoate (Ia).</p> <p>PREPARATION E.g. (1)</p>  <p>opt. base opt. iodide salt</p>	<p>W = leaving gp., e.g. Cl, Br, tosyloxy etc. (2) When X is other than a direct bond (i.e. X = X¹):</p>  <p>(3) For X = X² = O or S:</p>  <p>US4992433-A+/2</p>
---	--

dehydrate
→ (I; X = X²)

Reaction is in presence of PPh₃ and diethyl azodicarboxylate.

(4)



→ (I; X = X¹)

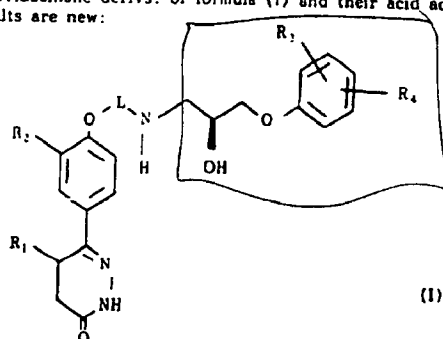
W¹ = leaving gp., e.g. F, Cl, Br, or NO₂.

EXAMPLE

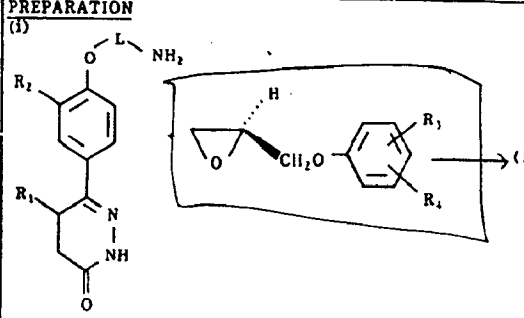
A mixt. of 10.4 pts. of 2-chloro-6-methylpyridazine, 22.4 pts. of ethyl 4-(2-(4-piperidinyl)ethoxy)benzoate butanedioate (1:1), 8.6 pts. Na₂CO₃, and 0.9 pts. DMF was stirred for 3 hrs. at 150°C. Work-up gave 17 pts. (56.8%) of (Ia) m.pt. 130.1°C (3:1 iPr₂O/acetone). (32ppi762CKDwgNo0/0).

US4992433-A/3

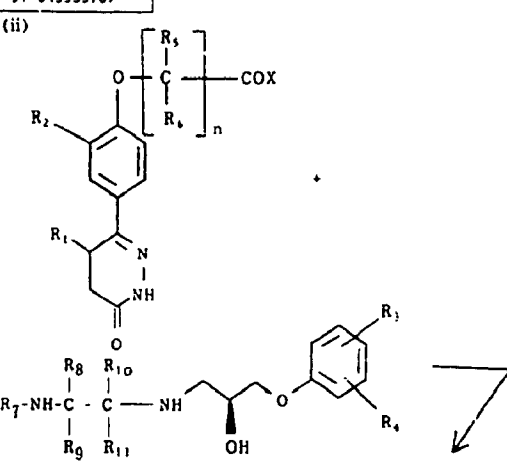
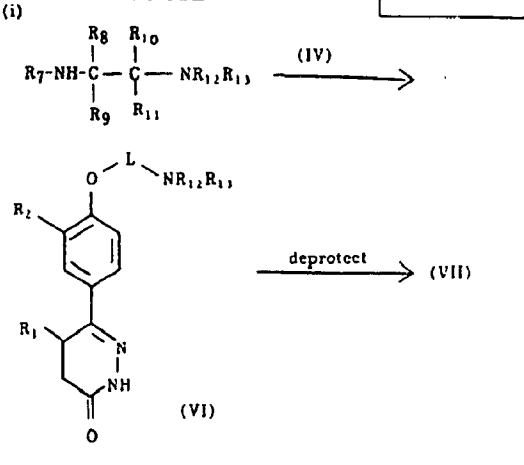
BEST AVAILABLE COPY

<p>91-045935/07 803 GLAXO 10.08.89 GLAXO INC *EP -412-814-A 01.09.89-US-402179 (+US-392233) (13.02.91) A61k-31/50 C07d-237/04 New pyridazinone derivs. have beta blocking activity for treatment of congestive heart failure C91-019457 R/AT BE CH DE DK ES FR GB GR IT LI LU NL SE1</p>	<p>B(7-D10, 12-E2, 12-E6B, 12-F1B)</p>
<p>Pyridazinone derivs. of formula (I) and their acid addn salts are new:</p>  <p>(I)</p>	<p>$R_1 = \text{H or lower alkyl};$ $R_2 = \text{H, halo, CF}_3, \text{CN, lower alkyl or lower alkoxy};$ $L = (\text{CR}_3\text{R}_4)_n \text{CON}(\text{R}_7)\text{CR}_8\text{R}_9\text{CR}_{10}\text{R}_{11}$ (gp. (a)) or $(\text{CR}_3\text{R}_4)_p$ (gp. (b)); $R_5 - R_{11} = \text{H or lower alkyl};$ $n = 1-4;$ $p = 2-6;$ $R_3, R_4 = \text{H, alkoxy, morpholino, CN, halo, CF}_3, \text{alkyl, alkylsulphonyl, alkoxyalkyl, cycloalkylalkoxyalkyl, NO}_2, \text{OH, alkenyloxy, NH}_2 \text{ or mono- or di-alkylamino.}$</p> <p>MORE SPECIFICALLY $R_1 = \text{H or Me};$ $R_2 = \text{H or Cl};$ $L = \text{(a)};$ $n = 1 \text{ or } 3;$ $R_3 - R_9 = \text{H};$ $R_{10}, R_{11} = \text{H or Me};$ $R_5 = \text{H};$ $R_4 = \text{CN, Cl or Me.}$</p>

EP-412814-A*

<p>USE (I) are useful for treating congestive heart failure. In tests (I) exhibit inotropic and β-adrenergic blocking activity. Dose is 0.1-5 mg/kg 1-4 times a day.</p> <p>SPECIFICALLY CLAIMED 4 Cpd. (I) e.g. 6-(4-(N-(2-(2-cyanophenoxy)-2-hydroxypropylamino)-2-methylpropyl)carbamoylmethoxy-3-chlorophenyl)-4,5-dihydro-3(2H)-pyridazinone; and 6-(4-(N-(2-(3-(2-cyanophenoxy)-(2S)-hydroxypropylamino)ethyl)carbamoylpropoxy-3-chlorophenyl)-4,5-dihydro-3(2H)-pyridazinone.</p> <p>WIDER DISCLOSURE Intermediates of formula (VI) (see 'Starting Materials') and (VII) (see 'Preparation') are new.</p>	<p>PREPARATION (I)</p>  <p>(VII)</p>
---	---

EP-412814-A*/1

<p>91-045935/07</p> <p>(ii)</p>  <p>(I; L = (a))</p>	<p>STARTING MATERIALS (i)</p>  <p>(IV)</p> <p>deprotect</p> <p>(VI)</p> <p>(VII)</p>
---	--

EP-412814-A*/2

$R_{12} = H$;
 R_{11} = amino protecting gp.;
or $R_{12} + R_{11}$ = divalent amino protecting gp.

EXAMPLE

A soln. of 499 mg 6-(4-(2-aminoethylcarbamoyl-methoxy)phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone and 208 ml (2S)-(+)-3-phenoxy-1,2-epoxypropane in 10 ml MeCN is refluxed for 10 hr. then evapd. The residue is taken up in $CHCl_3/MeOH$ (1:1) (10ml) then flash chromatographed over silica gel eluting with $CHCl_3/MeOH$ (90:10) (500 ml) then $CHCl_3/MeOH/NH_4OH$ (90:10:2) (1 l) to give 423 mg (60%) 6-(4-(N-(2-(3-phenoxy-2-hydroxy-propylamino)ethyl)carbamoylmethoxyphenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone (1a).

This is dissolved in 15 ml EtOAc. 5 ml ether are added. 12 ml 0.1 N Maleic acid in ether are added with stirring. The ppt. is filtered, washed with ether and dried overnight at 50°C in vacuo to give (1a) maleate, m.pt. 58-73°C (59pp985EDDwgNo0/0).

(E) ISR: No Search Report.

EP-412814-A /3

88-149149/22

803

ROBN 21.11.86

B(7-D5, 12-A7, 12-D2, 12-D6, 12-K2, 12-L4) N(1-A1)

ROBINS A H CO INC

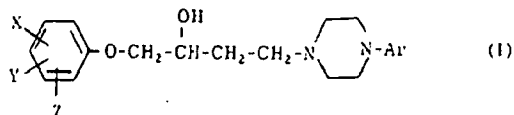
*EP -269-383-A

21.11.86-US-933180 (01.06.88) A61k-31/49

1-Phenoxy-4-(4-arylpiperazinyl)-2-butanol - used esp. in medicament for combatting type I allergic response in host

C88-066435 R(BE CH DE FR GB IT LI NL)

Use of a 1-phenoxy-4-(4-arylpiperazinyl)-2-butanol of formula (I) in the prepn. of a medicament for combatting Type I allergic response in a host is new.

Ar = -C₆H₄(X')(Y')(Z') or 2-, 3- or 4-pyridyl;X, X' = H, 1-8C alkyl, 1-8C alkoxy, halogen, CF₃, NO₂, NH₂, MeCONH, Ph, X'', Y''C₆H₃, MeCO, CN, CONH₂, COOH or (1-8C)alkoxycarbonyl;

Y, Y', Y'' and X'' = X substit. other than opt. substd. Ph;

Z, Z' = H, 1-8C alkyl or 1-8C alkoxy.

A salt and/or hydrate of (I) may also be used.

MORE SPECIFICALLY

Y = H, 1-8C alkyl or halogen;

Z = H, 1-8C alkyl or NO₂;

Y' = H, halogen or 1-8C alkoxy.

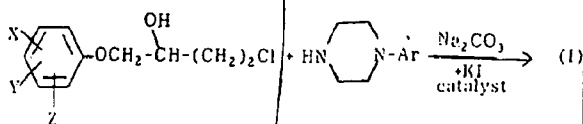
The use of 50 specific cpds. (I) is claimed, including 1-(2-chlorophenoxy)-4-(4-phenyl-1-piperazinyl)-2-butanol (Ia).

USE

(I) cause a decrease in the release of histamine and antagonise and organ effects of mediators involved in the immediate hypersensitivity response. They are therefore useful for treating allergic asthma, rhinitis, atopic dermatitis, chronic hives and allergic conjunctivitis.

Dose is 4-160 mg daily.

EP-269383-A+

PREPARATIONEXAMPLE

4-chlorophenoxy)-2-hydroxybutyl chloride (33.1g), N-phenylpiperazine (32.6g) and i-PrOH (400 ml) were refluxed together for 48 hrs., then kept overnight at 0°C and filtered.

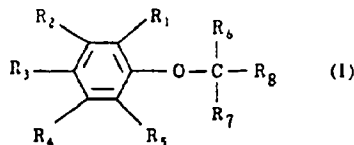
The filtrate was treated with HCl/Et₂O and Et₂O, and the solid prod. was sepd., dissolved in dil. HCl and neutralised with aq. NaOH to give 3.6g of (Ia), m.pt. 100-101.5°C after recrystn. from i-PrOH. (30pp1248HDDwgNo0/0). (E)ISR: No Search Report.

EP-269383-A

87-130843/19 C02 CIBA 01.10.85
CIBA GEIGY AG EP-221-844-A
01.10.85-CH-004245 (13.05.87) A01n-43/40 C07d-213/30
New 1-phenoxy-2-pyridyl-alkanone and-alkanol derivs. - useful as
fungicides, bactericides and plant growth regulators
C87-054365 (A T B E C H D E S F R G B G R I T L I L U M L S E)

C(7-D4, 12-A1, 12-A2C, 12-P1, 12-P9) 3

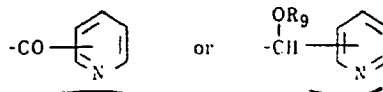
Phenoxyalkyl-pyridine derivs. of formula (1) are new:



$R_1 - R_5 = H$, halo, 1-6C alkyl or 1-6C alkoxy (both opt. substd. by halo), CN, 1-6C alkoxy-carbonyl or phenyl;

R_6 and $R_7 = H$, 1-6C alkyl, 3-6C alkenyl, 3-6C alkynyl, or phenyl or benzyl (both opt. ring-substd. by halo, 1-6C alkyl or 1-6C alkoxy, both opt. substd. by halo);

$R_8 =$



$R_9 = H$, 1-6C alkyl, 3-6C alkenyl, 3-6C alkynyl, or benzyl (opt. ring-substd. by halo, 1-6C alkyl or 1-6C alkoxy, both opt. substd. by halo); provided that the CO gp. in R_8 must be in the 3- or 4-position when R_1, R_2, R_4, R_5 and R_7 are all H, $R_3 = MeO$ and $R_6 = Me$; and R_9 can also be $R_{10}CO$; $R_{10} = 1-6C$ alkyl (opt. substd. by halo), 3-6C alkenyl or alkynyl, 2-5C alkoxy-alkyl, 3-6C cycloalkyl (opt. substd. by 1-3C alkyl) or phenyl, benzyl or phenethyl (opt. ring-substd. by halo, 1-6C alkyl or alkoxy, both opt. substd. by halo).

USE/ADVANTAGE

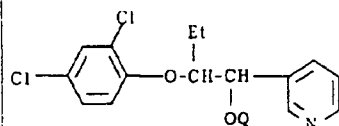
(1) are microbicides, effective against phytopathogenic bacteria and fungi; they have curative, systemic and esp.

EP-221844-A

preventative properties and can be applied to plants, seeds or soils. Some (1) also have plant-growth regulating activity and at higher doses inhibit excessive vegetative growth of crops. Pref. application rates are 150-600 g/ha.

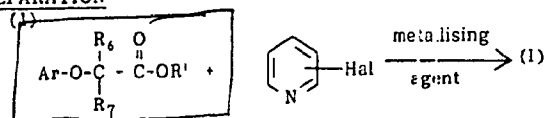
SPECIFICALLY CLAIMED

9 Cpds. e.g.



$Q = H, Me, MeCO$ or $MeO.CH_2.CO$.

PREPARATION

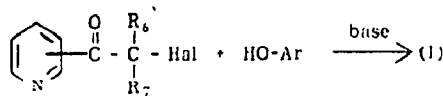


$Ar =$ phenyl substd. by R_1 to R_5 ;

$R' = 1-4C$ alkyl, 3-4C alkenyl, or phenyl or benzyl, opt. substd. by alkyl, alkoxy, halo, NO_2 or CN.

Reaction is pref. at -130 to $20^\circ C$, with Mg (in the form of a Grignard reagent) or BuLi as metallising agent.

(2)



Reaction is pref. at $0-120^\circ C$.

Both methods produce ketones which can be reduced conventionally to alcohols and these opt. alkylated or acylated.

EXAMPLE

140.2 g 93% 2,4-dichlorophenyl and 232 g K_2CO_3 were mixed in 1 l acetone, then heated briefly to boiling, cooled to $0^\circ C$ and gradually treated over 1 hr. with 224.8% 3-(bromoacetyl)pyridine hydrobromide.

The mixt. was stirred for 15 hr. at $0-5^\circ C$ and for 6 hr. at $20^\circ C$, then filtered and the mixt. evaporated. Recrystn. of the residue from MeOH gave 2-(2,4-dichlorophenoxy)-1-(3-pyridinyl)-1-ethanone, m.pt. $118-9^\circ C$. (31pp1251DAHDwgNo0/0).

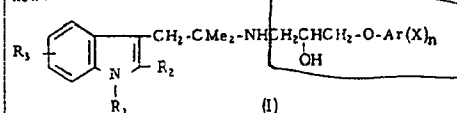
(G) ISR: DE2742173 EP-117485 DE2909754.

EP-221844-A

88281 C/49 B02 MEAD 13.07.77
MEAD JOHNSON CO *US 4234-595
29.01.79-US-007525 (+815138) (18.11.80) A61k-31/40 C07d-
209/12

1-Indolyl-butyl-amino-3-aryloxy-2-propanol derivs. - useful as
antihypertensives with vasodilator and adrenergic beta-blocking
action

Indole derivs. of formula (I) and their acid-addn. salts are
new:



(One of R₁ and R₂ is H and the other H or 1-4C alkyl;
R₃ is H, halo, 1-4C alkyl or alkoxy and is in the 4-, 5-, 6-
or 7-posn.;

Ar is Ph or naphthyl;

X is alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy,
alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy,
alkylsulphonyl, alkylsulphinyl, alkylthio, alkanoylamino,
alkenoylamino, alkoxy-carbonyl, alkenyloxy-carbonyl, alkoxy-
carbonylamino, alkoxy-carbonylaminoalkyl, cycloalkyl having
3-6 ring members and opt. substd. by 1-3 alkyl, cycloalken-

yl having 4-6 ring members and opt. substd. by 1-3 alkyl,
cycloalkylalkyl having 3-6 ring members and opt. substd. by
1-3 alkyl, cycloalkenylalkyl having 4-6 ring members and
opt. substd. by 1-3 alkyl, each of these substituents having
up to 8C; or CF₃, NO₂, NH₂, OH, halogen, CONH₂, CN, 2-4C
cyanoalkyl or 2-4C aminocarbonylalkyl;

n is 0, 1 or 2; or

Ar(X)_n is 4-indenyl, 6,7-dihydroxy-5,6,7,8-tetrahydro-1-
naphthyl or 5-oxo-5,6,7,8-tetrahydro-1-naphthyl)

USES

(I) are antihypertensive agents having adrenergic β-
blocking and vasodilator activities. They are also antiang-
inal, antistress, antiarrhythmic and antithrombogenic agents
and are useful for reducing the oxygen demand of the heart.
Dose is 0.1 μg-100 mg/kg (LD₅₀ values are 125->2000 mg/
kg orally in the mouse).

SPECIFICALLY CLAIMED

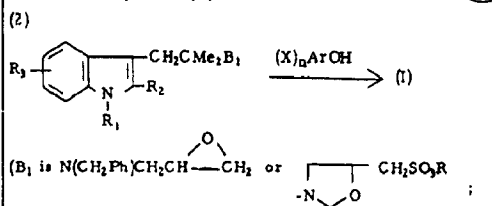
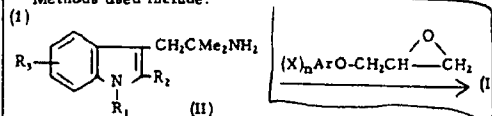
65 Cps. (I) e.g. 1-[2-(3-indolyl)-1,1-dimethylethyl]
amino-3-(2-methylphenoxy)-2-propanol and 2-[2-hydroxy-
3-[2-(5-methoxy-1H-indol-3-yl)-1,1-dimethylethyl]
amino]propoxy]benzonitrile hydrochloride.

88281C

US4234595+

PREPARATION

Methods used include:



R is 1-4C alkyl).

EXAMPLE

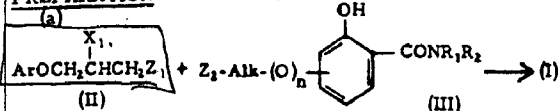
18.3 g 2-[2-(2,3-Epoxy)propoxy]benzonitrile and 15.2g
2-(3-indolyl)-1,1-dimethylethylamine in 500 ml EtOH was

refluxed overnight, then the mixt. was concd. to 200 ml.
The mixt. was cooled and the solid was sepd. and purified
to give 2-[2-hydroxy-3-(2-(3-indolyl)-1,1-dimethyl-
ethyl)amino]propoxy]benzonitrile, m.pt. 185-7°C as HCl
salt. (19pp1248).

US4234595

68119 C/39 CIBA GEIGY AG 01.03.79-CH-002037 (17.09.80) C07c-103/26 C07c-125/06 C07c-127/15 C07c-147/06 C07c-149/18 3-amino-1,2-propanediol 1-aryl ether derivs. - used as beta-adrenergic blockers or stimulants for treating cardiac disorders	B05 CIBA 01.03.79 *EP--15-505	B(7-H1, 7-H2, 10-B2, 12-E2, 12-E6, 12-E7, 12-F1, 12-F2, 12-F5) 5' 47
D/S: E(BE, CH, DT, FR, GB, IT, LU, NL, OE, SW). 3-Amino-1,2-propanediol derivs. of formula (I) and their salts are new.		activity for cardiac (β_1) receptors. They can be used as positive inotropic agents, esp. as cardiotonics for treating cardiac muscle insufficiency (opt. in combination with cardiac glycosides etc.), and also for treating cardiac rhythm disorders. Dose is 0.01-1 mg/kg p.o. Other cpds. (I) have β -blocking activity, possibly with intrinsic sympathomimetic activity. Cpds. with a p-substituent show good cardiac selectivity, while cpds. with an o-substituent have less cardiac selectivity and also have α -blocking activity. The β -blocking cpds. can be used for treating angina pectoris and arrhythmia, and as hypotensives. Dose is 0.03-3 mg/kg p.o. (I) are also intermediates for other cpds., esp. drugs.
$\text{ArOCH}_2\text{CHOHCH}_2\text{NH-alk-(O)}_n\text{-C}_6\text{H}_3(\text{OH})(\text{CONR}_1\text{R}_2) \quad (\text{I})$ <p>(Ar is opt. subst., aryl (including heteroaryl)); n is 3 or 1; alk is 2-SC alkylene with ≥ 2 C in the chain between the NH and the phenyl or phenoxy gp.; R₁ and R₂ are each H or lower alkyl; or they together form lower alkylene opt. interrupted by O, S, N or N-lower alkyl).</p> <p>USES Some cpds. (I), esp. those with Ar = hydroxyphenyl, have β-adrenergic stimulant activity with high selectivity.</p>		<p>SPECIFICALLY CLAIMED 18 Cpds. (I), e.g. 1-(2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino)-3-(4-(2-methoxyethoxy)-phenoxy)-2-propanol; 4-(2-hydroxy-3-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino)-propoxy-phenylacetamide; 1-(2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino)-3-(2-(pyrrol-1-yl)-phenoxy)-2-propanol; 1-(2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino)-3-(2-(2-methyl-indol-4-yl)-2-propanol; and 5-(3-(2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino)-2-hydroxy-propoxy)-1,2,3,4-tetrahydro-2,3-cis-naphthalene-diol. EP--15505+</p>

PREPARATION

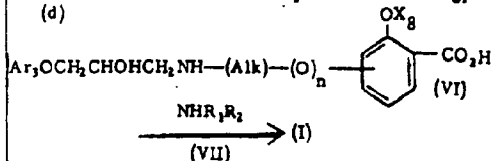


(one of Z₁ and Z₂ is reactively esterified OH, the other is NH₂ and X₁ is OH; or X₁ and Z₁ together are epoxy and Z₂ is NH₂).

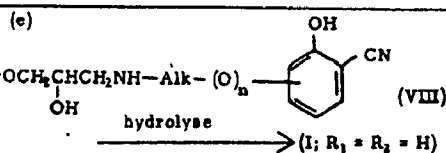
(b) Precursors with protected hydroxy gps. can be deprotected to give (I).

(c) Imino (Schiff base) precursors with =N- or -N= in the side-chain instead of -NH- can be reduced to (I), opt. with simultaneous reductive deprotection of OH gps.

(d)



(Ar₂ is as Ar or an Ar gp. contg. 1 or 2 gps. which can be aminolysed to OH; X₈ is H or an aminolysable protecting gp.)



OH gps. in (VIII) may be protected by hydrolyseable gps.

EXAMPLE

A mixt. of 11.2 g 1-(2-allyloxy-phenoxy)-3-amino-2-propanol, 10.5 g 5-(2-oxo-propoxy)-salicylamide, 200 ml toluene and a few drops of acetic acid was refluxed until water sepn. ceased (2-3 hrs.). The residue was dissolved in 300 ml EtOH. 5.7 g NaBH₄ was added in portions with stirring. The mixt. was stirred 2 hrs. at 20-30°C, left to stand overnight, adjusted to pH 3-4 with HCl, filtered and evapd. The residue was partitioned between 100 ml water and 100 ml EtOAc. The aq. phase was made alkaline with NH₄OH and extd. with 200 ml EtOAc. The organic phase was worked up to give an enantiomer mixt. of 1-(2-allyloxy-phenoxy)-3-(2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethylamino)-2-propanol as an oil. Slow crystn. from i-PrOH gave the pure enantiomer pairs, m. pt. 123-125°C and 98-102°C. (91pp941). (G) IER: D82032642; DT2357849. EP--15505